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New Applications of Organocatalysis

James Edward Taylor

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Chemistry

November 2011

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Science is the belief in the ignorance of experts.

RICHARD P. FEYNMAN

Abstract

New applications of organocatalysis, in particular the use of the bicyclic amidine DBN (1,5-diazabicyclo[4.3.0]non-5-ene) and then iodide as nucleophilic catalysts for Friedel-Crafts reactions, have been investigated.

Firstly, the use of amidines and guanidines as nucleophilic catalysts is reviewed. Amidines and guanidines are traditionally thought of as strong, non-nucleophilic bases. However, there is increasing evidence to suggest that amidines and guanidines are actually strong nucleophiles and can act as catalysts in a number of reactions.

The development of the first organocatalytic Friedel-Crafts acylation reaction is then described. It was found that DBN catalyses the regioselective *C*2-acylation of pyrroles and *C*3-acylation of indoles using acyl chlorides. The protocol was shown to work for a wide range of aromatic and alkyl acyl chlorides, as well as for a number of protected pyrroles and substituted indoles. The synthetic utility of the methodology was demonstrated with the synthesis of the non-steroidal anti-inflammatory drug Tolmetin. Detailed mechanistic studies have confirmed that DBN acts as a nucleophilic catalyst in the reaction, forming an *N*-acyl DBN intermediate with the acyl chloride. The structure of the intermediate has been confirmed by X-ray crystallographic analysis of an *N*-acyl DBN species as its tetraphenylborate salt.

As the *N*-acyl DBN tetraphenylborate salt was found to be bench stable, the use of such salts as alternatives to acyl chlorides was investigated. A number of crystalline and air stable *N*-acyl DBN tetraphenylborate salts were synthesised and were shown to act as acylating agents towards a wide range of nucleophiles, including primary and secondary amines, sulfonamides, and alcohols. The DBN hydrotetraphenylborate side-product could be conveniently removed from the reaction mixtures by filtration, allowing pure acylated products to be isolated without the need for column chromatography.

Finally, whilst investigating the Friedel-Crafts acylation of pyrroles, it was found that lithium iodide was a highly active catalyst for the process. Preliminary mechanistic studies suggest that the iodide acts as a nucleophilic catalyst towards acyl chlorides to form an acyl iodide intermediate in the reaction.

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Abbreviations

Ac	Acetyl
Ar	Aryl
app.	Apparent
Bn	Benzyl
BTM	Benzotetramisole
Boc	*tert*-Butyloxycarbonyl
br.	Broad
Bu	Butyl
CDI	*N*,*N*'-Carbonyldiimidazole
CF_3-PIP	(*R*)-2-Phenyl-6-(trifluoromethyl)-2,3-dihydroimidazo[1,2-*a*]pyridine
COSY	Correlation spectroscopy
Cy	Cyclohexyl
°C	Degrees Celsius
d	Doublet
δ	Chemical shift
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBDMH	1,3-Dibromo-5,5-dimethylhydantoin
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DHPB	3,4-Dihydro-2H-pyrimido[2,1-*b*]benzothiazole
DMB	3,4-Dimethoxybenzyl
DMAP	4-(Dimethylamino)pyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diastereomeric ratio
ee	Enantiomeric excess
Et	Ethyl
equiv.	Equivalents
g	Grams
h	Hours
Hz	Hertz
HBTM	Homobenzotetramisole
HOBt	Hydroxybenzotriazole
^{i}	*iso*

J	Coupling constant
m	Multiplet
m	*meta*
Me	Methyl
mL	Millilitre
mol	Mole
MTBD	7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
NBS	*N*-Bromosuccinimide
^{n}Bu	*n*-Butyl
NMR	Nuclear magnetic resonance
Np	Naphthyl
Nuc	Nucleophile
o	*ortho*
p	*para*
Ph	Phenyl
PMB	*para*-Methoxybenzyl
ppm	Parts per million
Pr	Propyl
PTSA	*para*-Toluenesulfonic acid
q	Quartet
rt	Room temperature
s	Selectivity factor
s	Singlet
^{t}	*tert*
t	Triplet
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
Tf	Triflate
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
THF	Tetrahydrofuran
THTP	2,3,6,7-Tetrahydro-5*H*-thiazolo[3,2-*a*]pyrimidine
Ts	*para*-Toluenesulfonyl

1 Amidines and Guanidines as Nucleophilic Catalysts

1.1 Introduction

Amidines and guanidines are important classes of compound that are found within nature and also have many uses within organic chemistry.[1-8] For example, the amino acid arginine (**1**) has a guanidine side chain and a number of natural products contain amidine units, such as noformycin (**2**) that has been isolated as a metabolite from actinobacteria. The two functional groups are also found within medicinally active compounds. Pentamidine (**3**) contains two amidine units and is used to treat protozoan infections, whilst guanidine derived cimetidine (**4**) was the first blockbuster drug used to treat peptic ulcers (Figure 1).[2]

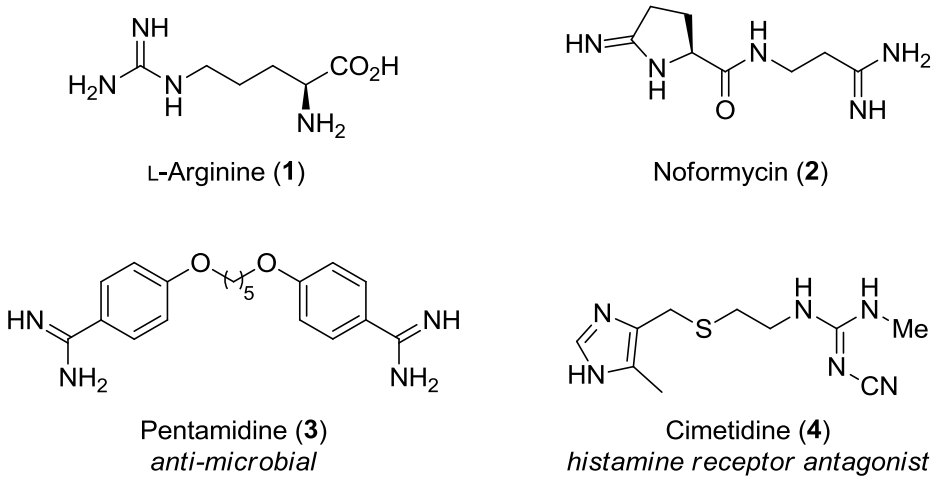


Figure 1. Examples of amidines and guanidines contained as fragments within natural products and drug molecules.

The most common use of amidines and guanidines in organic chemistry is as organic bases. They are some of the strongest neutral organic bases known due to the ability of their protonated forms to delocalise their charge over two nitrogen atoms. The structures and pK_as of some of the most commonly used amidine and guanidine bases are shown in Figure 2.[2,9] These bases have been used widely in numerous organic reactions and have often been shown to be advantageous over other organic bases. For example, the bicyclic amidines 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **5**) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, **6**) are often used as bases in dehydrohalogenation reactions as they allow alkene bonds to be formed under milder conditions than other nitrogen bases.[5] The physical properties of amidines and guanidines also make them useful *N*-based donor ligands in coordination chemistry.[4,10]

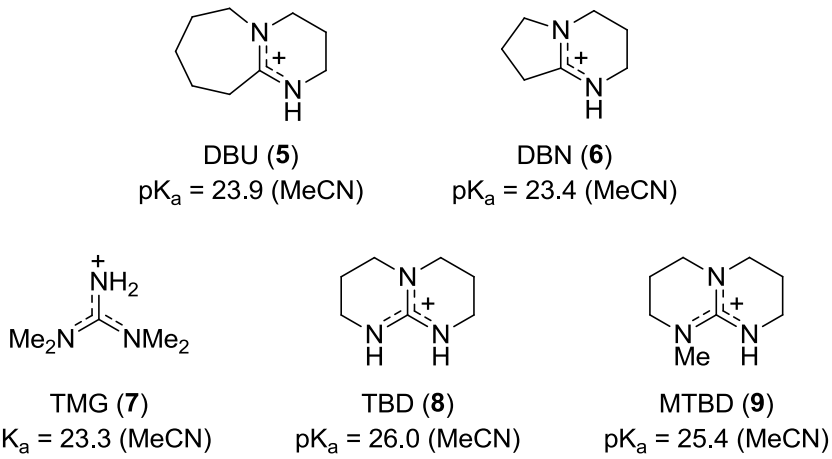
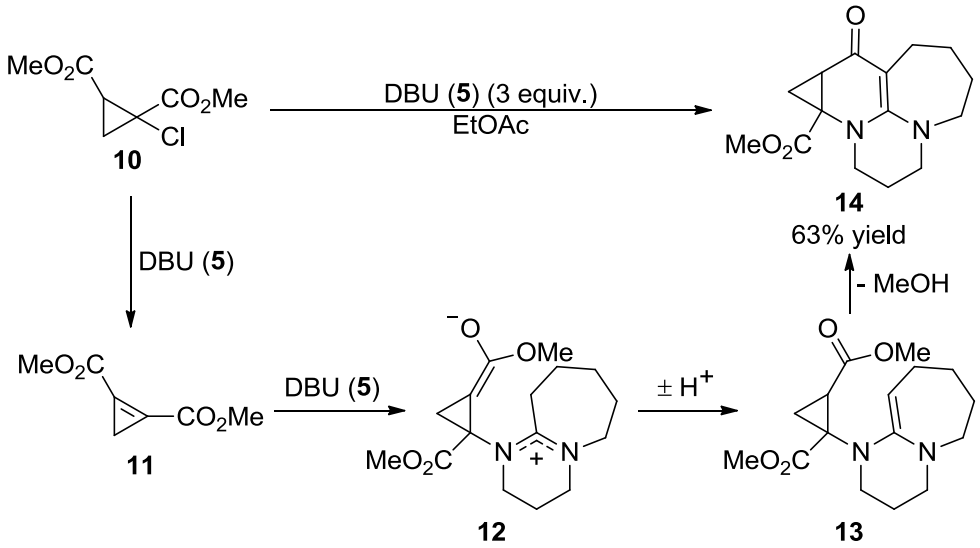


Figure 2. Structure and pK_as of some commonly used amidine and guanidine bases.

Traditionally, amidines and guanidines have been thought of as non-nucleophilic bases. However, with the recent increase in interest in organocatalysis,[11] a number of amidines and guanidines have been shown to act as nucleophilic catalysts in a wide range of reactions. A number of structurally related isothiourea derivatives have also been prepared based upon the promise of amidines and guanidines as acyl transfer catalysts. The remainder of this chapter will review the development of amidine, guanidine, and isothioureas that catalyse reactions by acting as nucleophiles.[3-4,12]

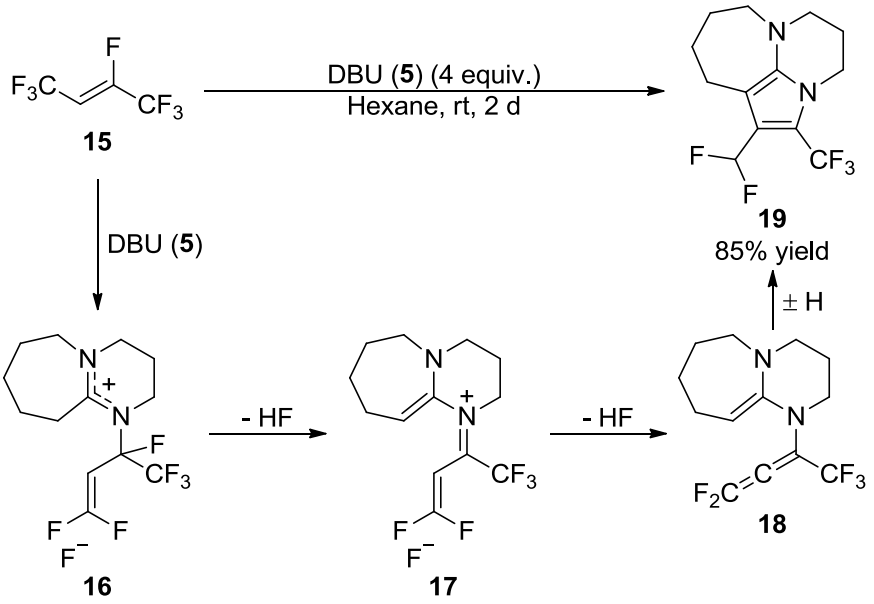
1.2 Nucleophilic Nature of Amidines and Guanidines

The amidine bases DBU (**5**) and DBN (**6**) have been widely used as bases in dehydrohalogenation reactions however, in some cases unexpected side-products were obtained from reactions. For example, in 1981 McCoy and Mal isolated and characterised an unusual tetracyclic dihydropyridin-4-one structure (**14**) from the dehydrohalogenation reaction of cyclopropane diester **10** using excess DBU (**5**) (Scheme 1). The authors postulated that the DBU (**5**) fragment was incorporated through nucleophilic attack of the α,β-unsaturated intermediate (**11**), although the generality of the process was not investigated further.[13]



Scheme 1. Unexpected tetracyclic side-product (**14**) isolated from the dehydrohalogenation reaction of cyclopropane diester **10** with DBU (**5**).[13]

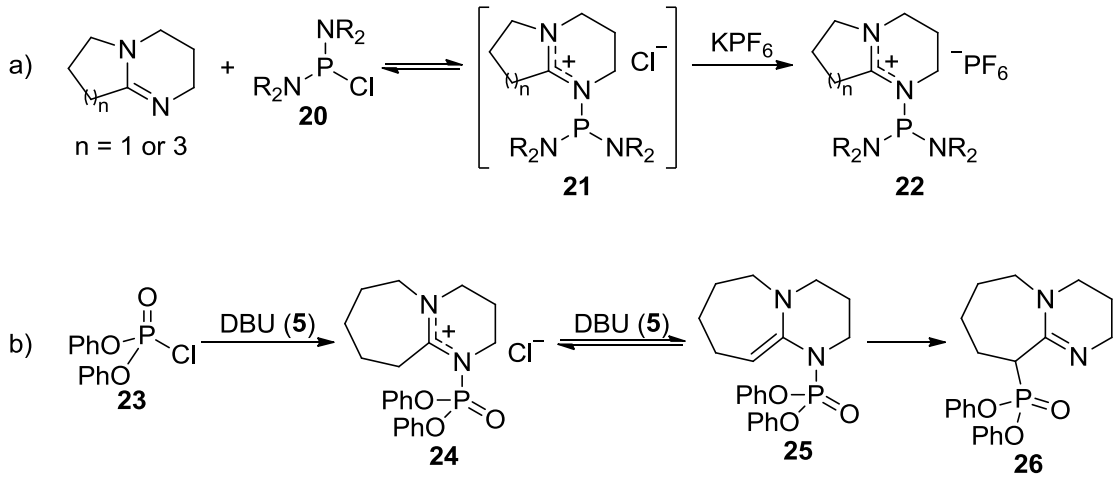
Subsequently, Chambers *et al*. found that DBU (**5**) reacts as a difunctional nucleophile towards 2*H*-heptafluorobut-2-ene (**15**) to form tricyclic pyrrole **19**, with excess DBU (**5**) helping to eliminate two equivalents of HF during the reaction (Scheme 2).[14] Sutherland and co-workers have also shown that DBU (**5**) reacts in a similar way with 3,5-dinitrobenzoate to form fused indole derivatives.[15]



Scheme 2. Reaction of DBU (**5**) with 2*H*-heptafluorobut-2-ene (**15**) to form tricyclic pyrrole **19**.[14]

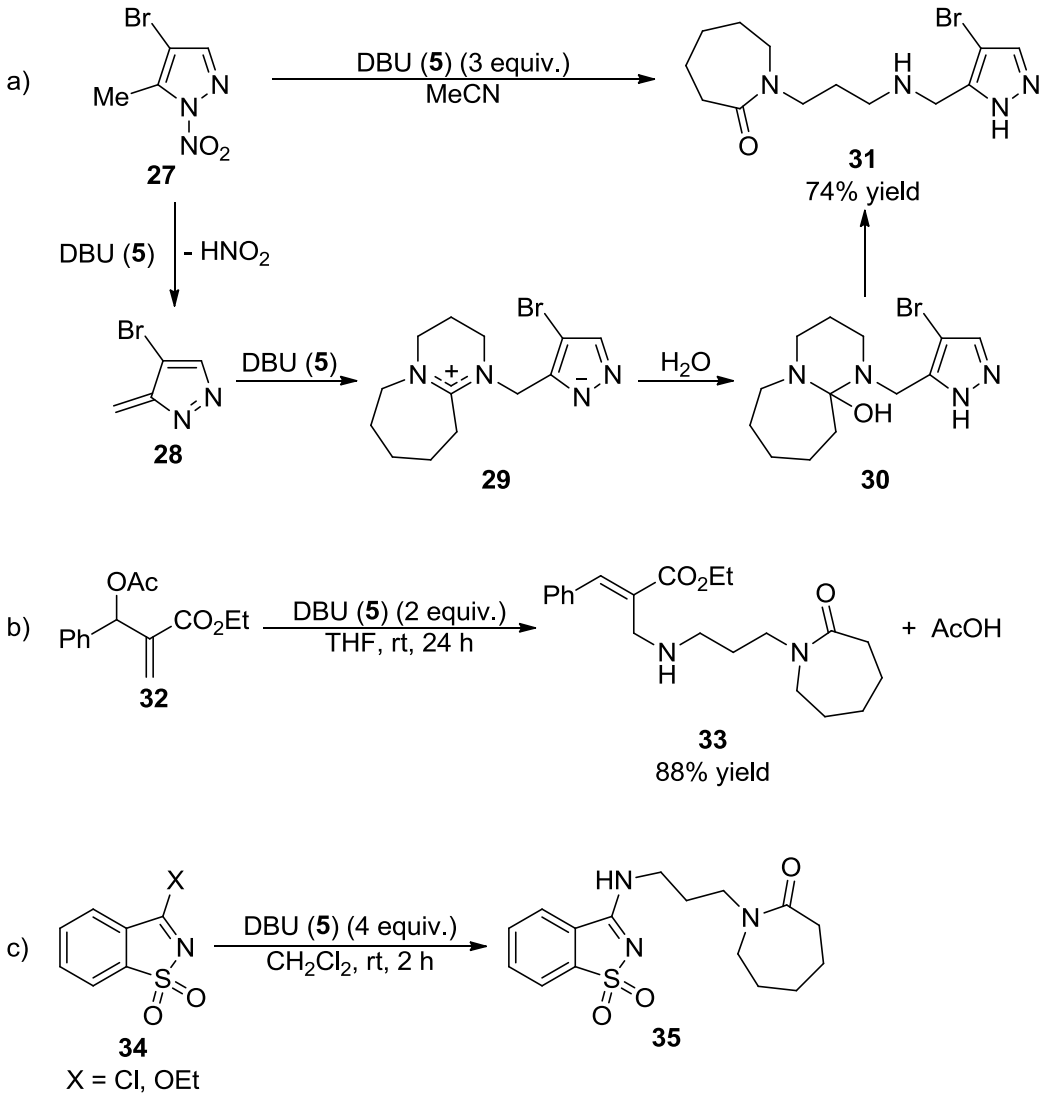
In 1993, Bertrand and co-workers were the first to state explicitly that DBU (**5**) and DBN (**6**) could act as strong nucleophiles. They showed that both DBU (**5**) and DBN (**6**) reacted with

chloro-phosphanes (**20**) to afford cationic phosphanes (**21**) that could be isolated and characterised if their chloride counter-ions were exchanged for hexafluorophosphate (Scheme 3a). An X-ray crystal structure of one of the cationic phosphanes (**22**) showed that both amidine C-N bonds were of similar length, suggesting that the positive charge was delocalised over both nitrogen atoms.[16] Stawinski *et al*. later showed that DBU (**5**) reacts with diphenylphosphoryl chloride (**23**) to form an *N*-phosphoryl adduct (**24**), which then undergoes an N→C phosphorus migration (Scheme 3b).[17]



Scheme 3. a) The first direct evidence that DBU (**5**) and DBN (**6**) can act as nucleophiles through reaction with chloro-phosphanes (**20**).[16] b) N→C phosphorus migration of *N*-phosphoryl DBU **24**.[17]

Subsequently there have been a number of reports of DBU (**5**) and DBN (**6**) being incorporated into molecules through nucleophilic addition. Lammers *et al*. were the first to show that bicyclic amidines could add to electrophilic carbon centres, demonstrating that they react with *N*-nitro-pyrazoles (**27**) to form lactam products (**31**) (Scheme 4a). Mechanistically, DBU (**5**) first acts as a base to eliminate HNO_2 from pyrazole **28**, with a second equivalent of DBU (**5**) acting as a nucleophile that adds to the exocyclic alkene of pyrazole **28**. The resulting intermediate (**29**) is then hydrolysed by adventitious water to form the ε-lactam product (**31**).[18] The formation of lactams *via* nucleophilic addition of DBU (**5**) or DBN (**6**) and subsequent hydrolysis of the charged intermediate has since been reported for reactions with α,β-unsaturated Baylis-Hillman adducts (**32**) (Scheme 4b)[19] and saccharin derivatives (**34**) (Scheme 4c), although in the latter case the lactam product (**35**) was a side-product observed when using saccharin derivatives (**34**) to catalyse the oxidation of sulphides.[20]



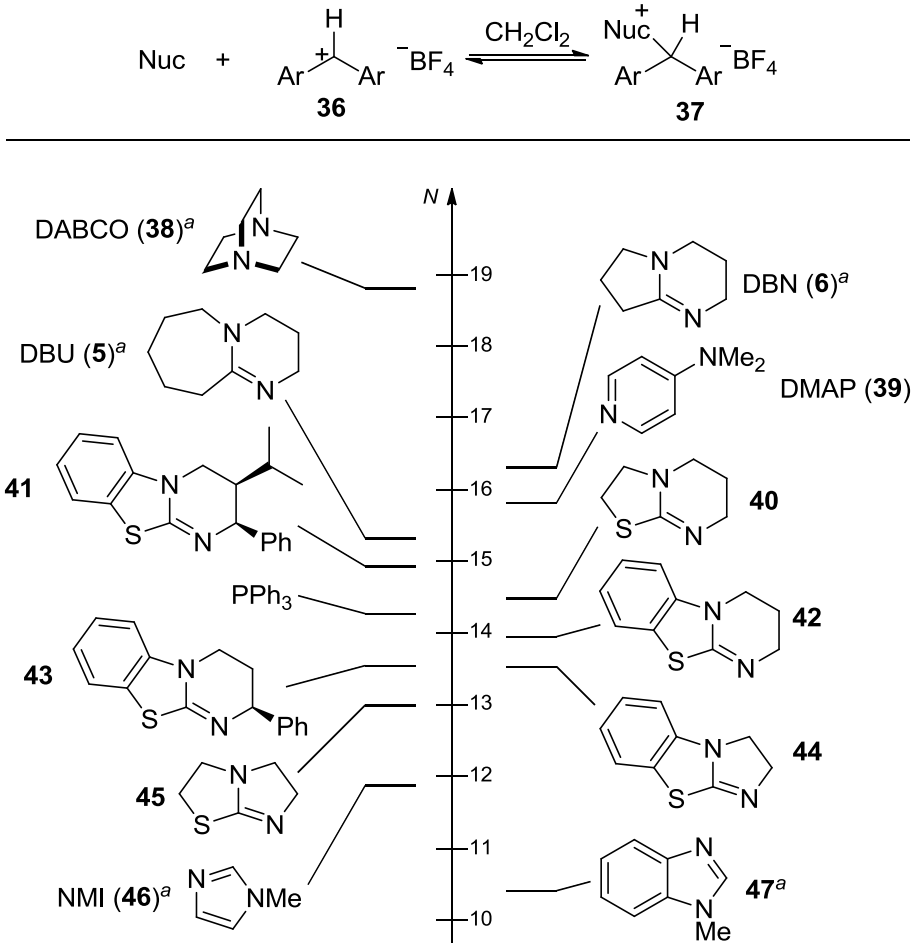
Scheme 4. a) Nucleophilic addition of DBU (**5**) to pyrazole (**28**) and subsequent hydrolysis reaction.[18] b) Addition/hydrolysis of DBU (**5**) to Baylis-Hillman adducts (**32**).[19] c) Addition/hydrolysis of DBU (**5**) to saccharin derivatives (**34**).[20]

Recently, Mayr and co-workers have performed a number of kinetic experiments to compare the nucleophilicity of DBU (**5**) and DBN (**6**) with other common organocatalysts, including isothiourea derivatives that have been shown to be effective acyl transfer catalysts (see page 7).[21-23] The equilibrium between a range of nucleophilic catalysts and a number of benzhydrylium tetrafluoroborate (**36**) anions was studied photometrically. The results of these kinetic experiments were analysed using Equation 1, where *k* is the second order rate constant, *s* is the nucleophile-specific slope parameter, *N* is the nucleophilicity parameter, and *E* is the electrophilicity parameter. This enabled the nucleophilicity parameter (*N*) of a number of organocatalysts to be compared directly (Scheme 5).[23]

$$\log k = s(E + N)$$

Equation 1. Nucleophilicity parameter (*N*) used to compare organocatalysts.

Remarkably, this study revealed that DBU (**5**), DBN (**6**), and recently synthesised isothiourea derivatives have comparable nucleophilicity to 4-(dimethylamino)pyridine (DMAP, **39**), which is one of the most commonly employed nucleophilic catalysts. DBN (**6**) was shown to be more nucleophilic than most of the catalysts studied, with only 1,4-diazabicyclo[2.2.2]octane (DABCO, **38**) exhibiting a greater *N* value.



Scheme 5. Relative nucleophilicities of selected nucleophilic catalysts. [a]Measurements made in MeCN. Scheme modified from reference 23.

Zipse *et al*. have performed an equally impressive study by calculating the methyl cation affinities of over 40 common organocatalysts.[24] Again, their computational method predicts that DBU (**5**), DBN (**6**), and bicyclic isothioureas have greater methyl cation affinities than many DMAP (**39**) derivatives, imidazoles, and cinchona alkaloids. Both studies revealed that bicyclic amidines (and presumably guanidines, although none were studied in either case) are

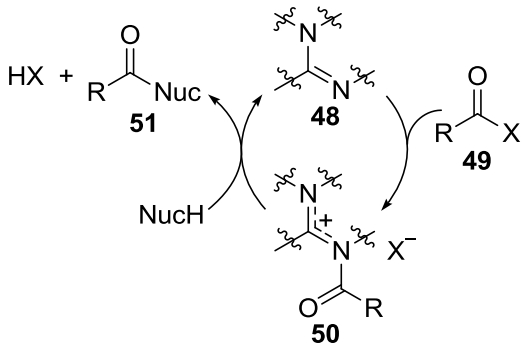
considerably more basic than many of the other organocatalysts studied. The relatively high basicity of these amines probably accounts for why they have received relatively limited attention as potential nucleophilic catalysts to date, because their use with acidic substrates can easily lead to deactivation by unwanted protonation.

1.3 Amidines and Guanidines as Nucleophilic Catalysts

Despite the potential problems associated with their high basicity, amidine, guanidine, and isothiourea derivatives have become increasingly popular catalysts due to their highly nucleophilic nature. The remainder of this chapter will focus on the uses of these types of catalysts in synthesis. Fu and Tan have recently reviewed the use of guanidines as catalysts, focusing on the mechanistic aspects of their reactions.[8]

1.3.1 Acyl Transfer Reactions

Acyl transfer is the most familiar reaction known to be accelerated by the use of nucleophilic catalysts. It is therefore unsurprising that a range of amidine, guanidine, and related isothiourea catalysts have been shown to be successful acyl transfer agents. A generalised mechanism for acyl transfer catalysed by amidine and guanidine derivatives is shown in Scheme 6. In most reactions, the catalyst (**48**) nucleophilically attacks the acyl donor (**49**) (usually an acyl chloride, acid anhydride, or an ester) to generate an activated *N*-acyl intermediate (**50**) that, due to its charged nature, is more reactive than the parent acyl donor (**49**). A nucleophile can then attack the *N*-acyl intermediate (**50**), forming an acylated product (**51**) whilst regenerating the catalyst (**48**).

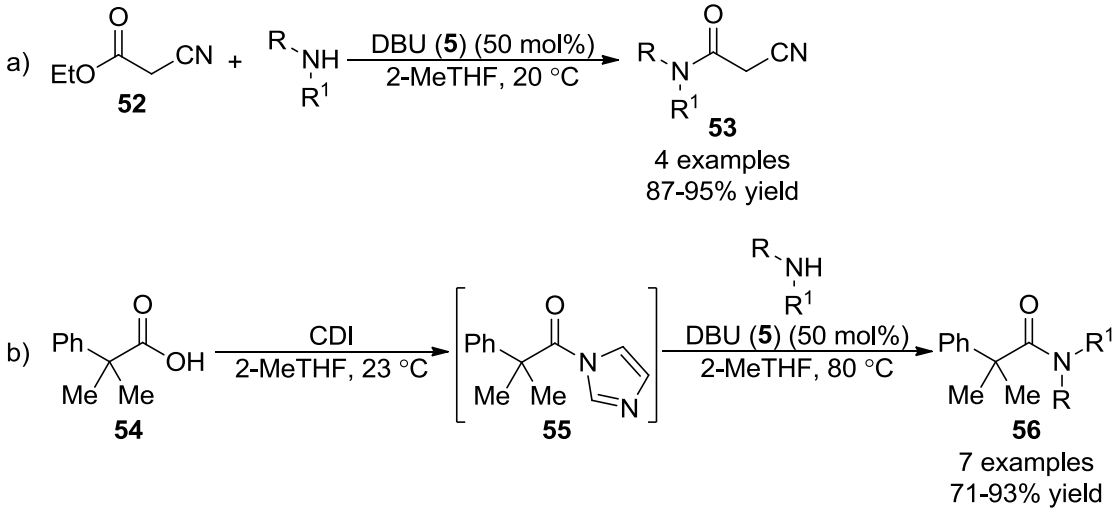


Scheme 6. General mechanism for acyl transfer catalysed by amidines and guanidines.

1.3.1.1 Amidations

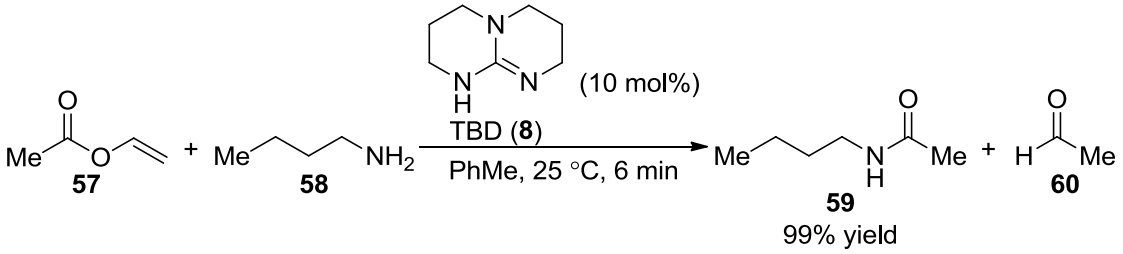
Vaidyanathan and co-workers have shown that DBU (**5**) is an efficient catalyst for amide formation from reactive esters and activated acids (Scheme 7). Initially the group found that

DBU (**5**) accelerated the rate of amidation of ethyl cyanoacetate (**52**) with a small range of secondary amines (Scheme 7a).[25] This methodology was extended by using DBU (**5**) to catalyse the addition of amines to acyl imidazole **55**, which was formed *in situ* from the reaction of 2-methyl-2-phenyl propanoic acid (**54**) with *N*,*N*'-carbonyldiimidazole (CDI) (Scheme 7b).[26] This sterically demanding substrate was chosen to demonstrate the efficiency of DBU (**5**) as a catalyst for difficult substrates and also to avoid side-reactions that could occur *via* α-deprotonation. It was found that the rate enhancement of amidation using DBU (**5**) was comparable with those observed with traditional additives to CDI-amidation reactions such as hydroxybenzotriazole (HOBt). Mechanistically, DBU (**5**) is thought to add nucleophilically to both ethyl cyanoacetate (**52**) and acyl imidazole **55** to generate *N*-acyl DBU intermediates that are more reactive towards amines than their parent substrates.



Scheme 7. DBU (**5**) catalysed amidations of a) ethyl cyanoacetate (**52**) and b) acyl imidazoles (**55**).[25-26]

Waymouth *et al*. have shown that 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, **8**) catalyses the formation of secondary amides from vinyl, benzyl and ethyl esters, as well as primary amides. For example, vinyl acetate (**57**) and butylamine (**58**) react to give an almost quantitative yield of *N*-butylacetamide (**59**) in only six minutes when using 10 mol% TBD (**8**), as compared with the 24 hours required for the uncatalysed process (Scheme 8). Kinetic studies suggest that TBD (**8**) reacts with the ester to form an *N*-acyl TBD intermediate, which is then nucleophilically attacked by the amine.[27]

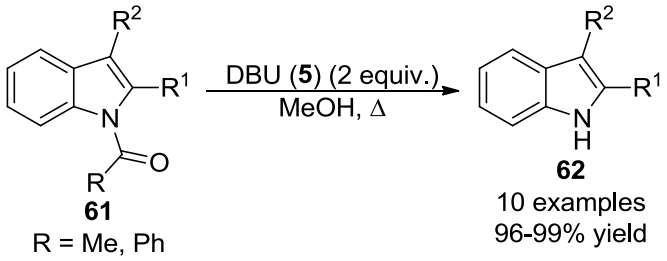


57 **58** **59** **60**

Scheme 8. Amidation of vinyl acetate (**57**) with butylamine (**58**) catalysed by TBD (**8**).[27]

Waymouth *et al*. have also shown that TBD (**8**) is an efficient catalyst for transesterifications and the ring-opening polymerisation of cyclic esters such as lactide, δ-valerolactone, and ε-caprolactone.[28] However, detailed mechanistic and computational studies predict that a hydrogen-bonding mechanism is favoured over nucleophilic catalysis in these cases.[27-30]

Chakrabarty *et al*. have found that amide bonds can also be cleaved using an amidine as a catalyst. A series of *N*-acetyl and *N*-benzoyl indoles (**61**) was deprotected by heating in methanol at reflux in the presence of two equivalents of DBU (**5**), forming the parent indoles (**62**) in high yields (Scheme 9).[31] Coin *et al*. also reported unexpected nucleophilic behaviour of DBU (**5**) towards peptide bonds, which limited its use as a base for the removal of Fmoc protecting groups in the total synthesis of the cyclic peptide cotransin.[32]



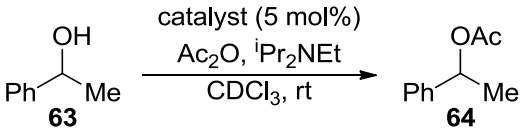
Scheme 9. Deprotection of *N*-acyl indoles (**61**) promoted by DBU (**5**).[31]

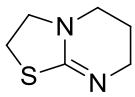
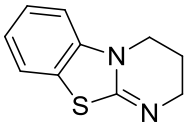
1.3.1.2 Esterifications

Okamoto *et al*. and Birman and co-workers have both investigated the use of amidine derivatives for the acylation of alcohols with acetic anhydride.[33-34] Selected results from Birman and co-workers studies on the acylation of 1-phenylethanol (**63**) with acetic anhydride using various nucleophilic catalysts are shown in Table 1. It was found that DBN (**6**) was much more reactive than DBU (**5**), with the rate of acylation comparable with that observed with DMAP (**39**) (Table 1, entries 1-3). A number of amidine derivatives were synthesised and tested in the reaction, with the isothioureas 2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyrimidine (THTP, **65**) and 3,4-dihydro-2H-pyrimido[2,1-*b*]benzothiazole (DHPB, **42**) proving to be more reactive than

DMAP (**39**) (Table 1, entries 4 and 5).[34] Direct evidence for nucleophilic catalysis was observed by Okamoto *et al*. when a 1:1 mixture of DHPB (**42**) and acetic anhydride was analysed by ^{1}H NMR spectroscopy, which showed the formation of significant amounts of an *N*-acetyl DHPB intermediate.[33] The increased reactivity of the isothiourea derivatives compared with the basic amidines has been attributed to increased stabilisation of the *N*-acetyl DHPB intermediate by nonbonded interactions between the sulphur and the carbonyl oxygen.

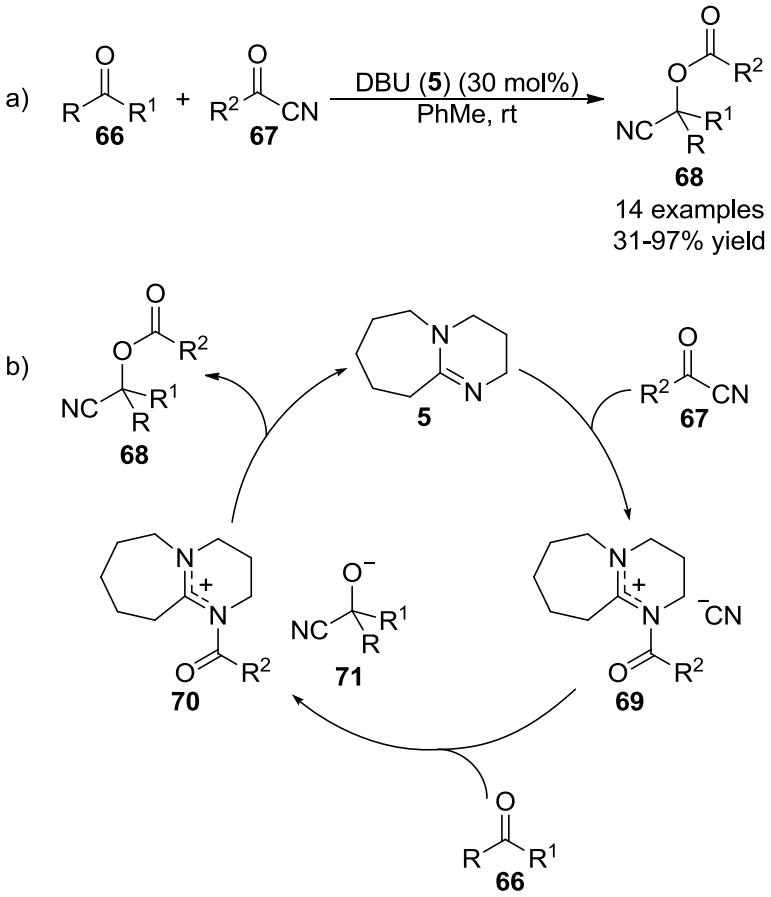
Table 1. Acylation of 1-phenylethanol (**63**) using amidine derivatives as catalysts.[a]



Entry	Catalyst	Substrate Conc. (M)	$t_{1/2}$[b]
1	DMAP (**39**)	0.1	5 min
2	DBN (**6**)	1	15 min
3	DBU (**5**)	1	17 h
4	 THTP (**65**)	0.1	2 min
5	 DHPB (**42**)	0.1	<2 min

[a]Data taken from reference 34. [b]Time to reach 50% conversion determined using ^{1}H NMR spectroscopy.

Shi and Zhang have shown that DBU (**5**) catalyses the cyanoacylation of ketones (**66**) with acyl cyanides (**67**) (Scheme 10a).[35] Mechanistically, DBU (**5**) is thought to add to the acyl cyanide (**67**) to generate an *N*-acyl DBU intermediate (**69**). The cyanide anion released during this addition can then undergo nucleophilic attack at the ketone (**66**) to give a cyanoalkoxide (**71**), which is then acylated by the *N*-acyl DBU species (**70**) (Scheme 10b).



Scheme 10. a) Cyanoacylation of ketones (**66**) by acyl cyanides (**67**) catalysed by DBU (**5**). b) Proposed mechanism.[35]

1.3.1.3 Kinetic Resolutions

A number of enantiomerically pure nucleophilic catalysts have been used as acylation catalysts for the kinetic resolution of a wide range of substrates and this area has been reviewed recently by both Schreiner *et al*.[36] and Pellissier.[37] Some of the most active amidine and isothiourea catalysts developed for kinetic resolutions are shown in Scheme 11.

Birman and co-workers have developed a number of excellent catalysts for the kinetic resolution of secondary alcohols. Firstly, the enantiomerically pure amidine derivative (*R*)-2-phenyl-6-(trifluoromethyl)-2,3-dihydroimidazo[1,2-*a*]pyridine (CF_3-PIP, **74**) was shown to be active in the kinetic resolution of benzylic secondary alcohols (**72**, R = alkyl, R^1 = Ar) with acid anhydrides.[38] It was found that the rate of acylation using catalyst **74** was increased by using one equivalent of $^{i}Pr_2NEt$, presumably by helping to prevent catalyst deactivation by any acid generated during the reaction. The highest selectivity factors (*s*) of up to 85 were observed for the acylation of benzylic secondary alcohols with propanoic anhydride. The proposed transition state for the reaction involves π-π or cation-π interactions between the aryl group of the alcohol

and the pyridinium ring of the catalyst. The favoured enantiomer for acylation is the one in which steric repulsions between the alkyl group of the alcohol and the acyl groups are minimised (Figure 3).

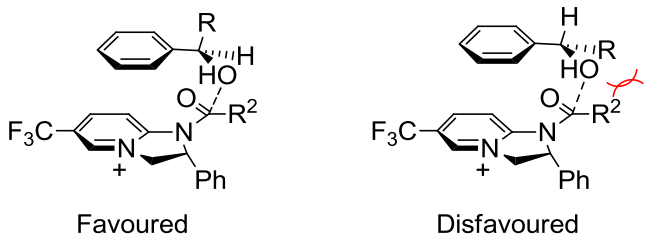
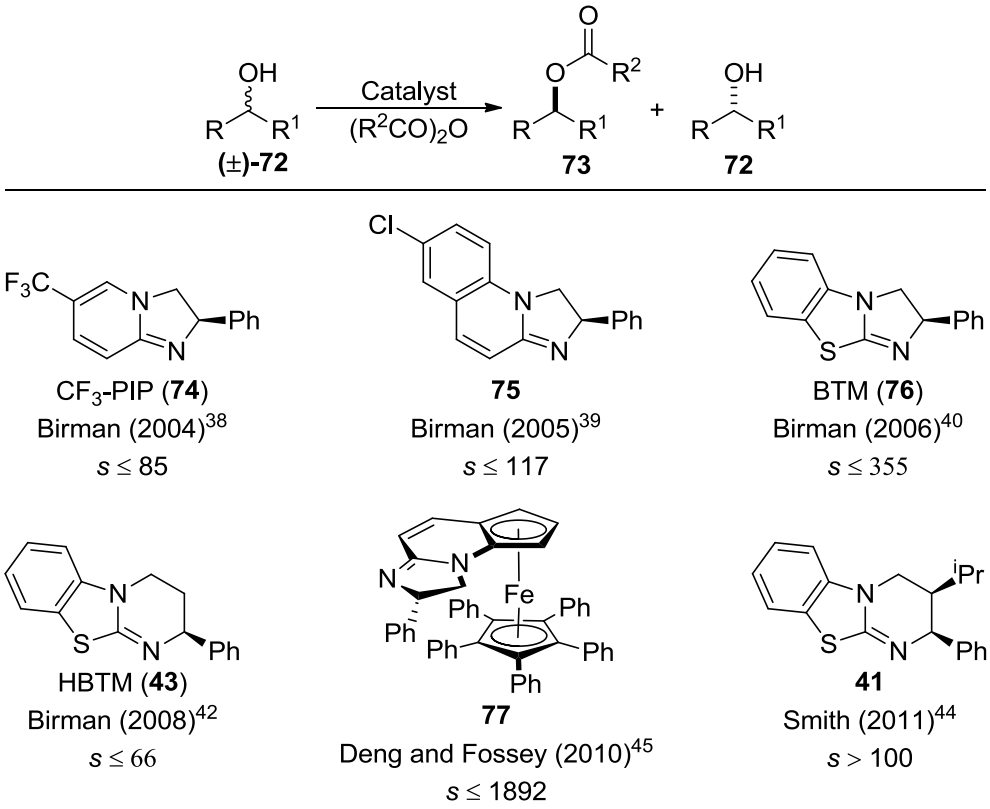


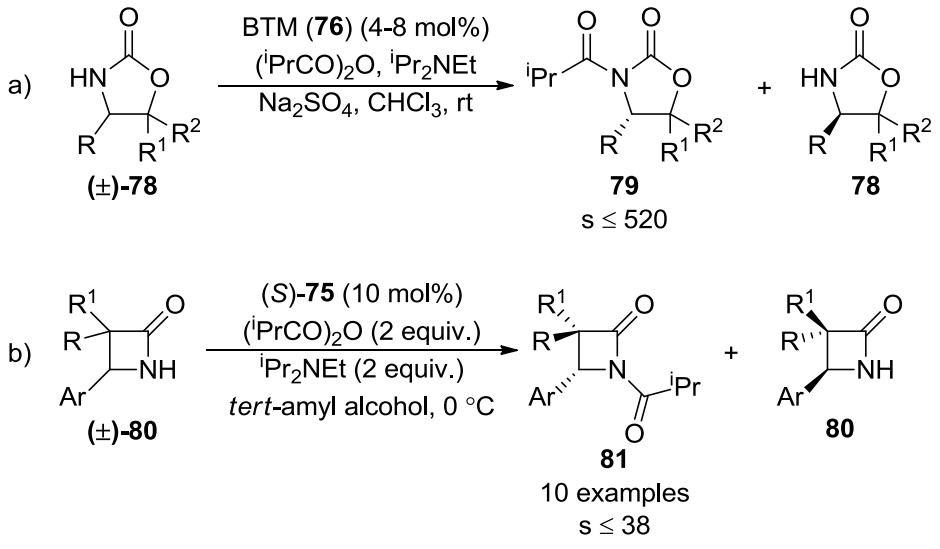
Figure 3. Proposed transition state for the resolution of aryl secondary alcohols using CF_3-PIP (**74**).[38]

Birman and co-workers then developed a new catalyst that contains an additional aryl ring (**75**) for the resolution of cinnamoyl based allylic alcohols. The extended π-system of **75** allowed efficient π-stacking between the alkene and remote aryl fragments of the allylic alcohols with the catalyst, giving high *s* values for the resolution of a number of substrates using propanoic anhydride.[39] In 2006, Birman *et al*. employed enantiomerically pure benzotetramisole (BTM, **76**) as a catalyst for the kinetic resolution of benzylic alcohols.[40] It was found that BTM (**76**) was highly active and, unlike previously developed catalysts (**74** and **75**), could be used with isobutyric anhydride as an acyl donor, which allowed *s* values of up to 355 to be obtained. BTM (**76**) was also shown to be an efficient catalyst for the resolution of propargylic alcohols. Although the *s* values of up to 32 were significantly lower than those observed for benzylic alcohols they represent the highest *s* values obtained for propargylic alcohols *via* a non-enzymatic resolution pathway.[41] Extending the imidazoline ring of BTM (**76**) by one carbon atom to give catalyst **43**, named homobenzotetramisole (HBTM), allowed a number of 2-aryl-substituted cycloalkanols to be resolved with *s* values of up to 66 observed.[42] Further substitutions to the HBTM (**43**) core by Birman *et al*.[43] and Smith *et al*.[44] have resulted in a number of catalytic variants that have been used as efficient catalysts for the kinetic resolution of benzylic, cinnamoyl, propargyl, and cyclic secondary alcohols with acid anhydrides. Recently, Fossey and Deng *et al*. combined the principles behind Fu's highly successful planar chiral DMAP catalysts with Birman's amidine catalysts to prepare catalyst **77**, which was shown to give remarkable *s* values of up to 1892 for the resolution of benzylic alcohols with propanoic anhydride.[45]



Scheme 11. Examples of amidine and isothiourea derivatives that have been used as catalysts for the kinetic resolution of secondary alcohols (**72**).

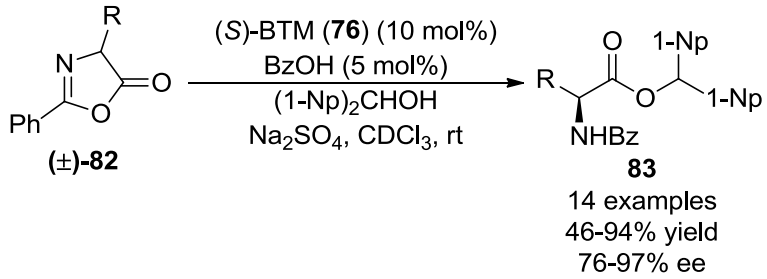
Birman and co-workers have also applied their amidine catalysts to the kinetic resolution of racemic 2-oxazolidinones (**78**) and 4-aryl-β-lactams (**80**) that proceed through an enantioselective *N*-acylation process (Scheme 12). It was found that BTM (**76**) was the most



Scheme 12. Kinetic resolution of a) 2-oxazolidinones (**78**) and b) 4-aryl-β-lactams (**80**) using catalytic, enantioselective *N*-acylation protocols.[46-47]

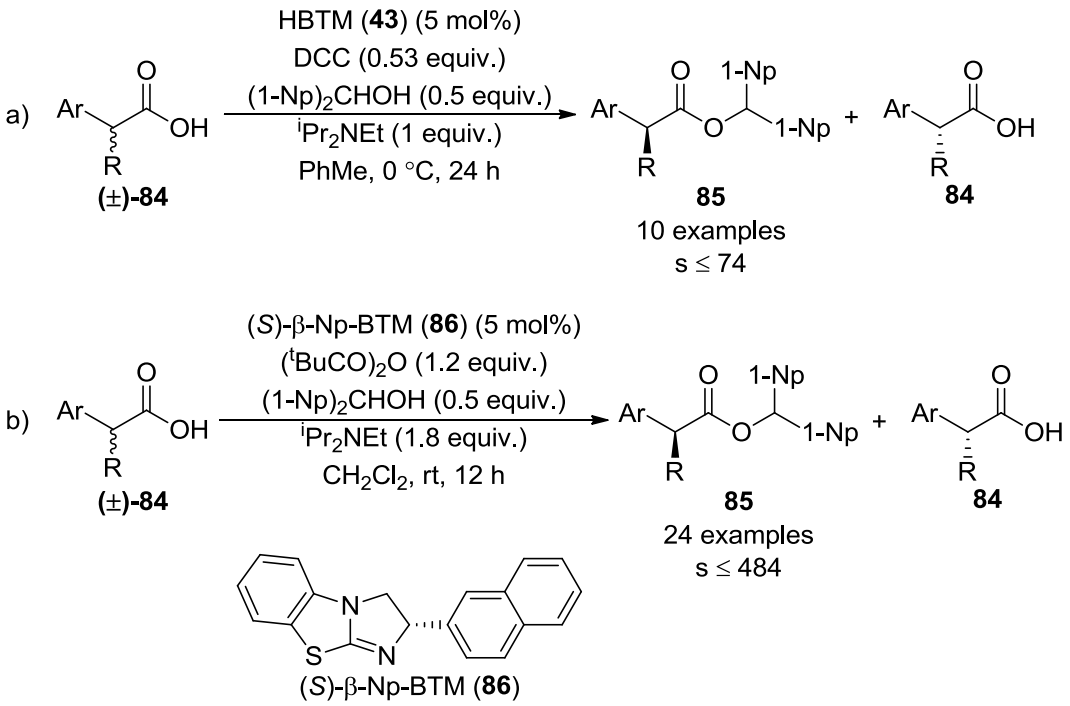
efficient catalyst for the kinetic resolution of 2-oxazolidinones (**78**) giving *s* values of up to 520 (Scheme 12a),[46] whilst catalyst **75** was optimal for the resolution of 4-aryl-β-lactams (**80**) (Scheme 12b).[47]

BTM (**76**) was also shown to be capable of catalysing the dynamic kinetic resolution of azlactones (**82**) to form α-amino acid derivatives (**83**) in high yields and good ee (Scheme 13).[48] The highest levels of enantioselectivity were observed using di(1-naphthyl)methanol as a nucleophile, which was rationalised by the increased steric demand of the alcohol and increased π-π interactions with the catalyst.



Scheme 13. Dynamic kinetic resolution of azlactones (**82**) using BTM (**76**) and di(1-naphthyl)methanol.[48]

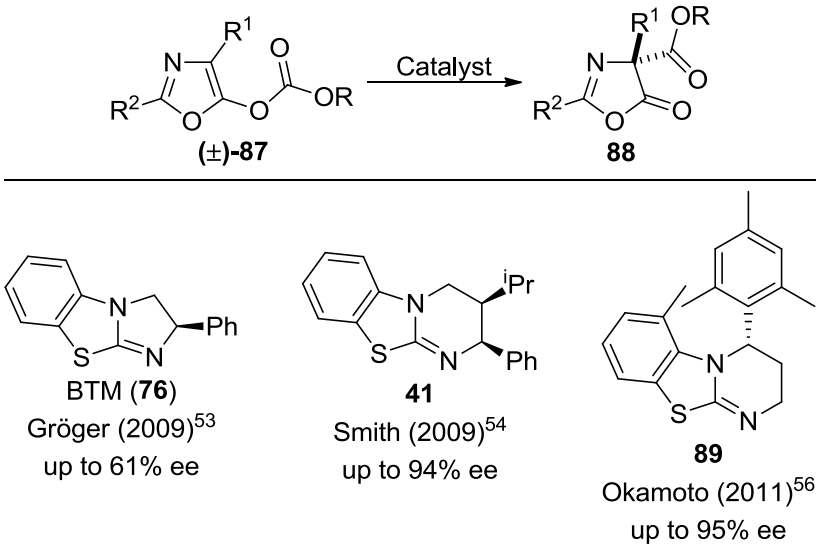
Isothiourea derivatives have also been used as catalysts for the kinetic resolution of α-aryl acids (**84**) (Scheme 14). Birman and co-workers employed half an equivalent of dicyclohexylcarbodiimide (DCC) to form a symmetrical anhydride of racemic acid (**84**) *in situ*, which was then kinetically resolved using HBTM (**43**) to provide the corresponding α-aryl esters (**85**) with high levels of enantioselectivity (Scheme 14a).[49] Shiina *et al*. have also used (*S*)-β-Np-BTM (**86**) for the kinetic resolution of mixed anhydrides generated *in situ* from pivalic anhydride and α-aryl acids (**84**) (Scheme 14b). The catalyst (**86**) was shown to be highly selective, with the highest *s* values of up to 484 observed for *ortho*-substituted α-aryl acids.[50-51]



Scheme 14. Kinetic resolution of α-aryl acids (**84**) using a) HBTM (**43**) and DCC and b) (*S*)-β-Np-BTM (**86**) and pivalic anhydride.[49-51]

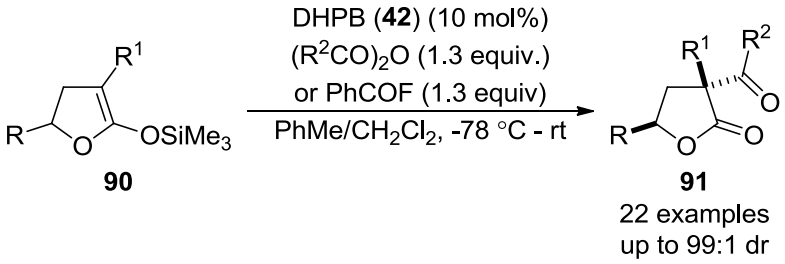
1.3.1.4 *C*-Acylations

Smith *et al*. initially demonstrated that the achiral isothiourea DHPB (**42**) efficiently catalysed the *O*- to *C*-acyl transfer reaction (Steglich rearrangement) of oxazolyl carbonates (**87**).[52] Gröger and co-workers subsequently showed that enantiomerically pure BTM (**76**) could be used to form 4-carboxyazlactone products (**88**) enantioselectively with reasonable ee (Scheme 15).[53] Smith *et al*. then reported that HBTM derivative **41** gave higher yields and improved enantioselectivities for this rearrangement compared with BTM (**76**).[54] Catalyst **41** could also be used for the stereoselective rearrangement of furanyl enol carbonates, affording a mixture of lactone regioisomers, whose major regioisomer of product could be isolated in reasonable yield with good levels of ee.[55] Recently, Okamoto and co-workers have developed DHPB derivative **89** and shown it to be an effective catalyst for the asymmetric rearrangement of oxazolyl carbonates (**87**), giving comparable enantioselectivities with those observed for the HBTM derivative **(41**).[56]



Scheme 15. Enantioselective *O*- to *C*-acyl transfer reactions of 5-oxazole carbonates (**87**) to their corresponding 4-carboxyazlactones (**88**).

Smith *et al*. have developed the first isothiourea catalysed intermolecular *C*-acylation reactions of cyclic silyl ketene acetals (**90**), which avoids competing *O*-acylation that is often observed with enols and enolates.[57] It was found that DHPB (**42**) catalyses the *C*-acylation of a range of cyclic silyl ketene acetals (**90**) with either acid anhydrides or benzoyl fluoride (Scheme 16). The cyclic β-keto esters (**91**) formed contain chiral quaternary carbon centres and the reaction was found to be highly diastereoselective with up to 99:1 dr observed.

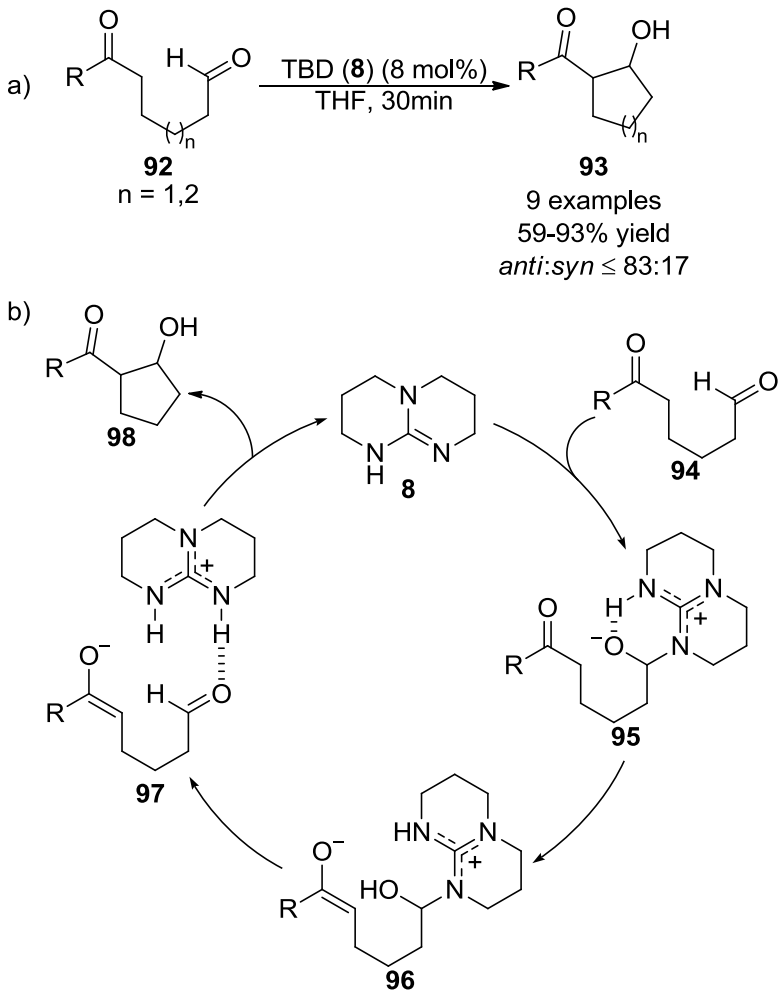


Scheme 16. DHPB (**42**) catalysed diastereoselective intermolecular *C*-acylation reactions of cyclic silyl ketene acetals (**90**).[57]

1.3.2 Aldol Reaction

Baati and co-workers found that the guanidine TBD (**8**) was an efficient catalyst for the intramolecular aldol reaction of keto-aldehydes (**92**), forming cyclic aldol products (**93**) in reasonable yields with modest levels of diastereoselectivity (Scheme 17a).[58] Whilst the cyclisation process could be promoted by TBD (**8**), the observation that 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD, **9**) and 1,1,3,3-tetramethylguanidine (TMG, **7**) were

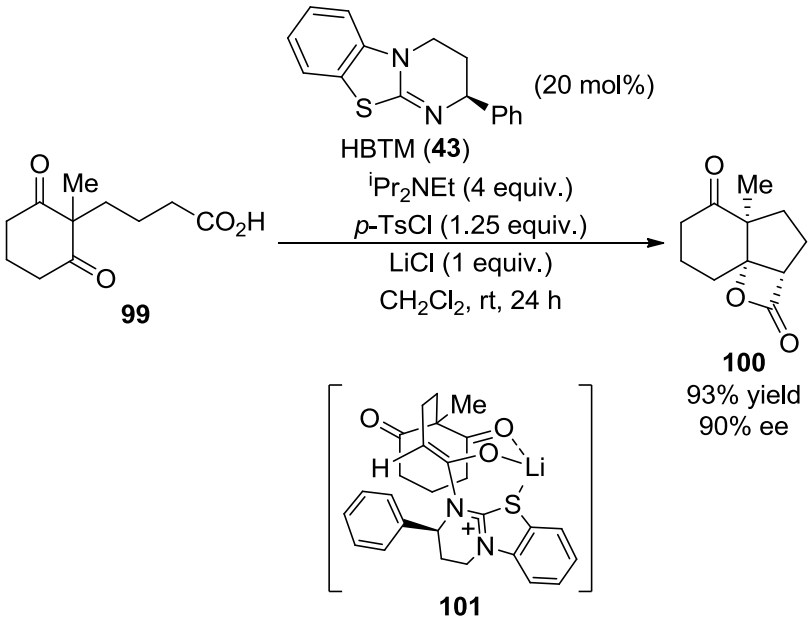
much less active despite their similar basicities led the authors to propose an alternative mechanism in which the TBD (**8**) acts as a bifunctional catalyst (Scheme 17b). They proposed that TBD (**8**) initially acts as a nucleophile towards the aldehyde (**94**) to form a stabilised tetrahedral intermediate (**95**). Intramolecular proton transfer forms the required enolate of the ketone (**96**), before the aldehyde is regenerated by release of a guanidinium cation. The guanidinium cation can then hydrogen-bond to the aldehyde (**97**) to activate it towards intramolecular nucleophilic attack.



Scheme 17. a) Intramolecular aldol reaction catalysed by TBD (**8**). b) Proposed mechanism.[58]

Romo *et al*. have shown that isothioureas can catalyse the intramolecular aldol-lactonisation of keto-acids to form bi- and tri-cyclic lactones.[59-60] For example, HBTM (**43**) was shown to catalyse the aldol-lactonisation of keto-acid **99** to form tricyclic lactone **100** in high yield with good levels of enantioselectivity (Scheme 18).[60] Mechanistically, the acid (**99**) is activated towards nucleophilic attack by HBTM (**43**) using *p*-TsCl to form an *N*-acyl HBTM intermediate, which can then be deprotonated to form the required enolate. It was found that

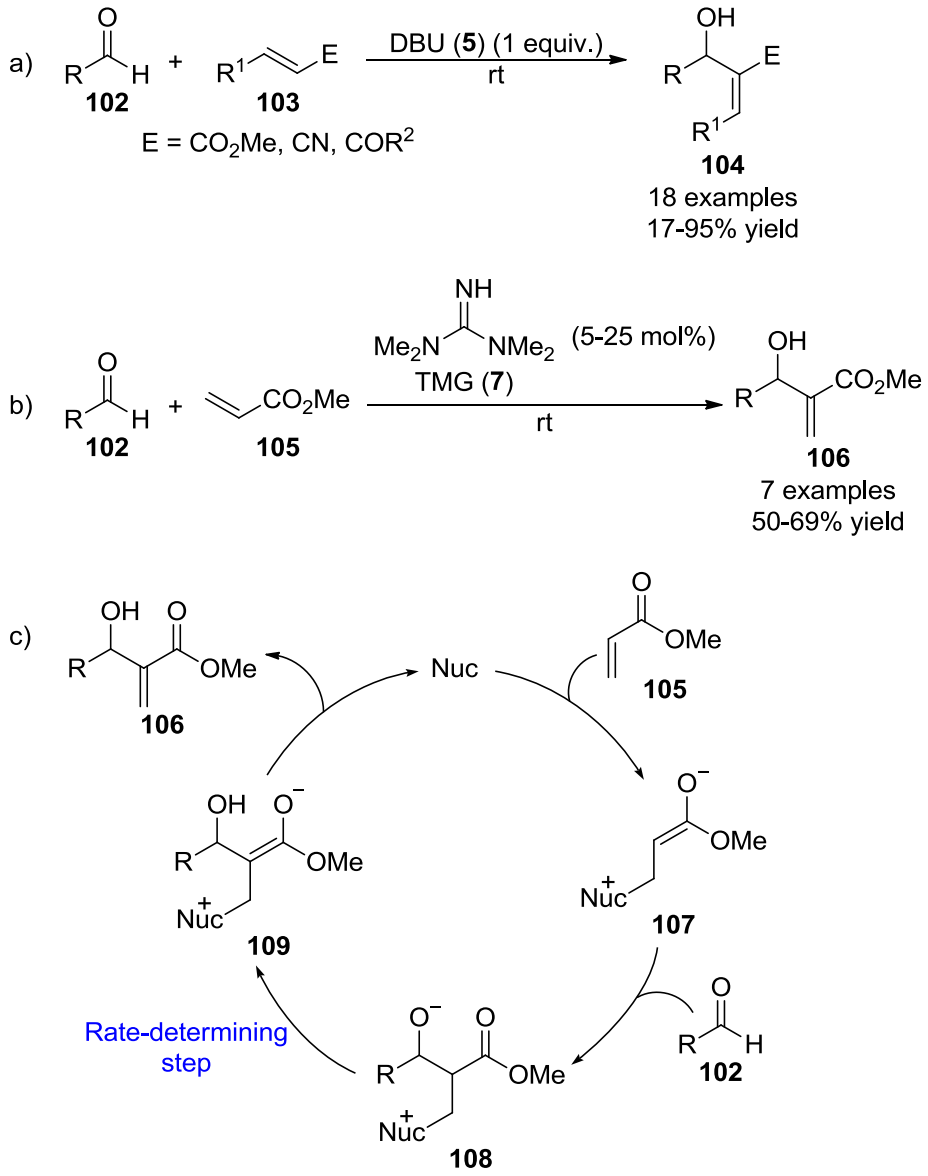
using one equivalent of LiCl increased the yield of the reaction, presumably by acting as a Lewis acid to chelate the enolate and ketone into a chair-like transition state that enables the aldol reaction to proceed (**101**).



Scheme 18. HBTM (**43**) catalysed intramolecular aldol-lactonisation reaction to form a tricyclic lactone (**100**).[60]

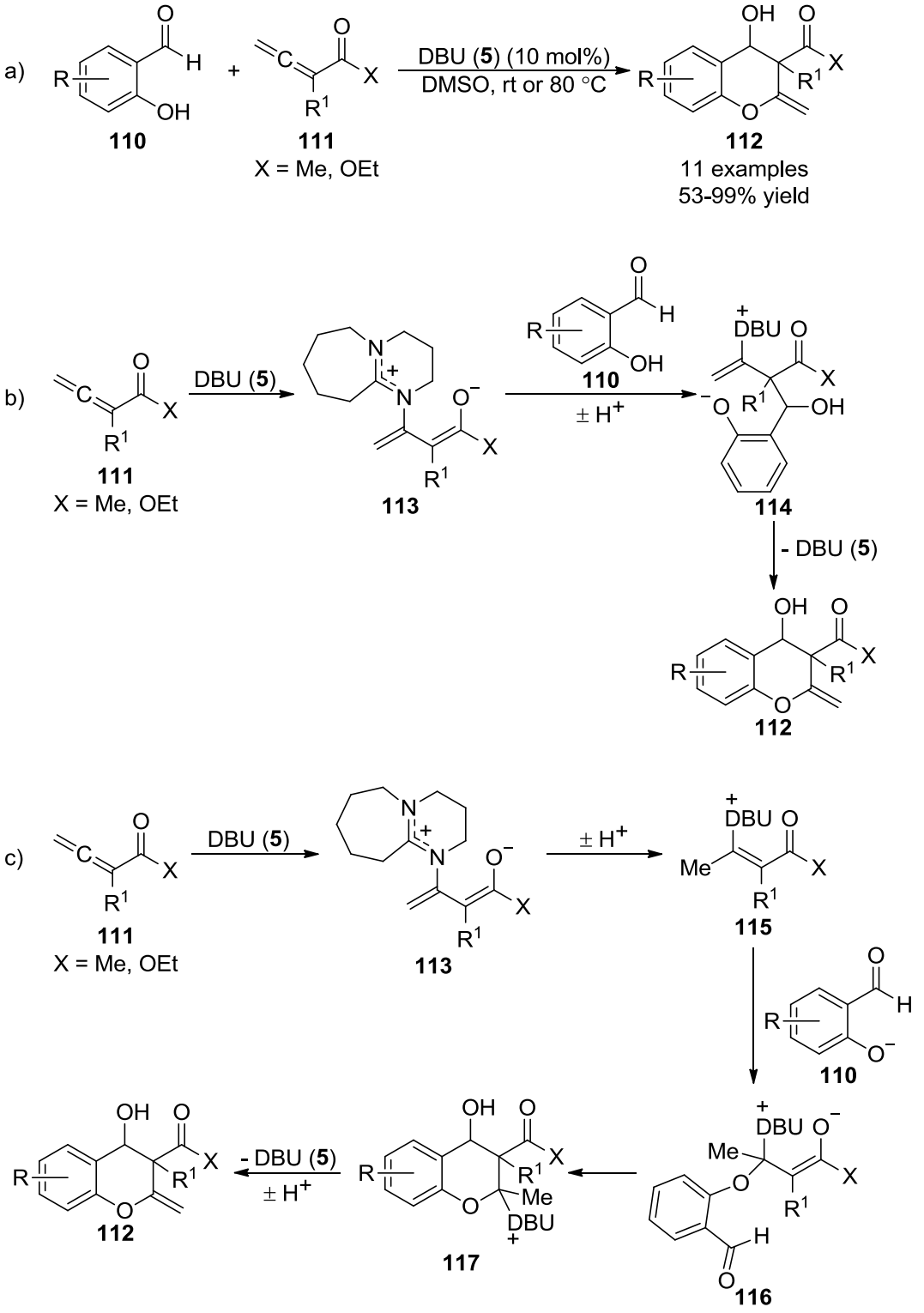
1.3.3 Morita-Baylis-Hillman Reaction

In 1999, Aggarwal and co-workers discovered that DBU (**5**) was an efficient catalyst for the Morita-Baylis-Hillman reaction, with rates of reaction faster than those observed with DABCO (**38**) (Scheme 19a).[61] Mamaghani *et al*. found that the rate of reaction could be further increased using an equivalent of lithium bromide alongside one equivalent on DBU (**5**).[62] Leadbeater and van der Pol showed that TMG (**7**) also catalyses the reaction between methyl acrylate (**105**) and a range of aldehydes (**102**) (Scheme 19b).[63-64] The rate-enhancement observed with DBU (**5**) and TMG (**7**) is attributed to increased resonance stabilisation of the β-ammonium enolate (**107**) formed from conjugate addition of the catalyst to the unsaturated substrate when compared with other tertiary amines (Scheme 19c). Cheng *et al*. subsequently found that DBU (**5**) catalysed the Morita-Baylis-Hillman reaction of sterically demanding substrates in methanol.[65] The strong solvent dependence of the reaction led Cheng *et al.* to propose that the methoxide anion was the true catalyst of the reaction using DBU (**5**) in methanol. However, detailed computational studies by Aggarwal and Harvey *et al*. suggested that methanol increases the rate of the tertiary amine catalysed Morita-Baylis-Hillman reaction by allowing the rate-determining proton-transfer step to occur *via* a lower energy concerted pathway.[66]



Scheme 19. Morita-Baylis-Hillman reactions catalysed by a) DBU (**5**) and b) TMG (**7**).[61,63-64] c) Proposed mechanism of the Morita-Baylis-Hillman reaction.

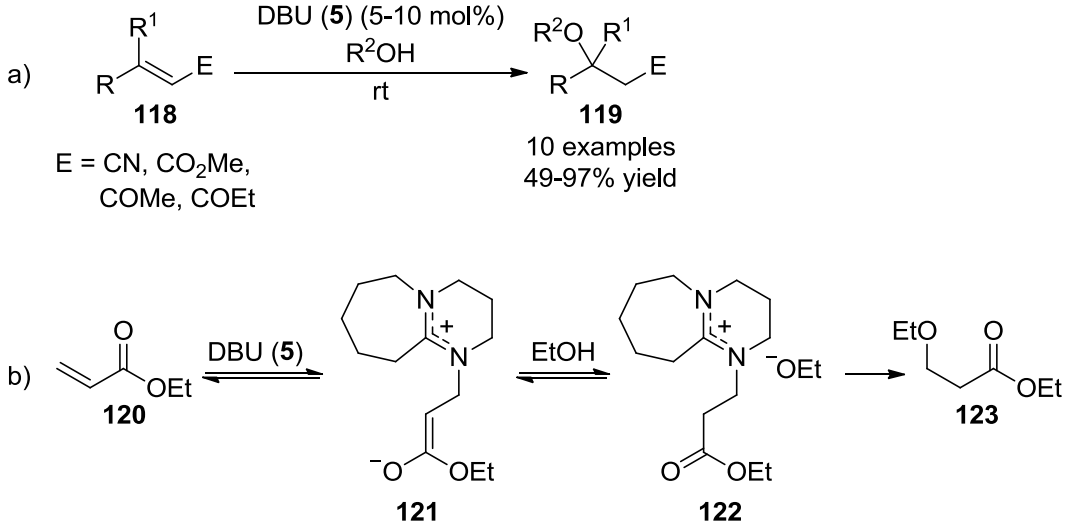
In a related process, Shi *et al*. have shown that 10 mol% DBU (**5**) can be used to catalyse the reaction between salicylic aldehydes (**110**) and allenes (**111**) to form 2*H*-1-chromenes (**112**) (Scheme 20a).[67] As observed with other α,β-unsaturated ketones, the DBU (**5**) is believed to activate the allene (**111**) through conjugate addition to form a β-ammonium enolate (**113**). Two potential cyclisation mechanisms may then occur. The β-ammonium enolate **113** could undergo a Morita-Baylis-Hillman reaction with the salicylic aldehyde (**110**) functionality followed by cyclisation to form the observed 2*H*-1-chromenes (**112**) (Scheme 20b). Alternatively, β-ammonium enolate **113** could be protonated and the salicylic aldehyde (**110**) can undergo a conjugate addition followed by an aldol reaction to form the products (**112**) (Scheme 20c).



Scheme 20. a) DBU (**5**) catalysed reaction of salicylic aldehydes (**110**) and allenes (**111**) to form 2*H*-1-chromenes (**112**). b) Potential mechanism *via* Morita-Baylis-Hillman reaction and cyclisation. c) Potential mechanism *via* conjugate addition and intramolecular aldol reaction.[67]

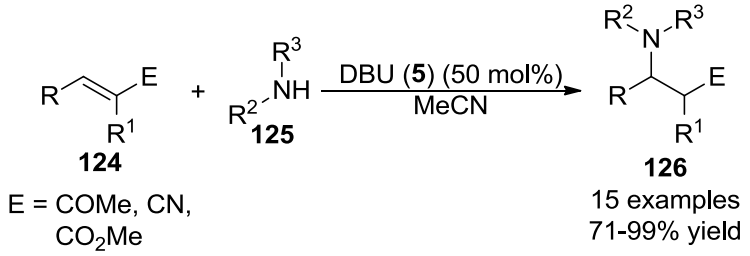
1.3.4 Conjugate Additions

Whilst screening tertiary amines as catalysts for the Baylis-Hillman reactions, Connon *et al*. observed a competing hydroalkoxylation reaction. This resulted in the development of a DBU (**5**) catalysed conjugate addition of alcohols to α,β-unsaturated nitriles, esters, and ketones (**118**) (Scheme 21a).[68] Mechanistically, the authors propose that the DBU (**5**) undergoes a conjugate addition to the α,β-unsaturated substrate (**120**) to generate a β-ammonium enolate intermediate (**121**), similar to those proposed for the Morita-Baylis-Hillman reaction. The enolate is then protonated by the alcohol solvent to generate a second charged DBU-intermediate (**122**) and an alkoxide anion. This alkoxide anion then undergoes an S_N2 reaction with the charged intermediate (**122**), with DBU (**5**) as the leaving group (Scheme 21b).



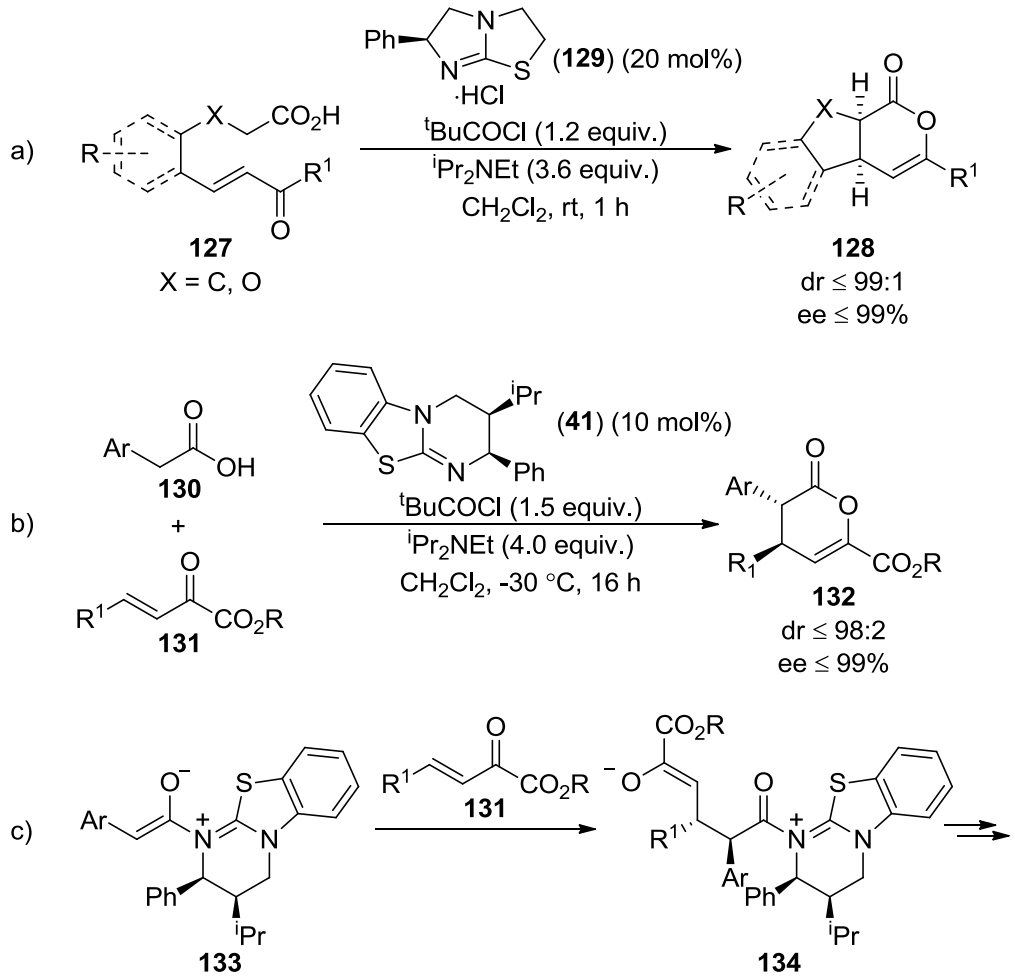
Scheme 21. a) DBU (**5**) catalysed conjugate addition of alcohols to α,β-unsaturated nitriles, esters, and ketones (**118**). b) Author's proposed mechanism for the addition of ethanol to ethyl acrylate (**120**).[68]

Kim and co-workers have shown that DBU (**5**) catalyses the aza-Michael addition of a range of amines (**125**) to α,β-unsaturated ketones, nitriles, and esters (**124**) (Scheme 22).[69] Although no mechanism is proposed, Kim and co-workers speculate that the reactivity cannot be explained by base catalysis alone. It is therefore possible that the reaction proceeds with a similar mechanism to that proposed by Connon *et al*. for their alcohol conjugate addition protocol (Scheme 21b).



Scheme 22. DBU (**5**) catalysed aza-Michael addition of amines (**125**) to α,β-unsaturated ketones, nitriles, and esters (**124**).[69]

Recently, Smith *et al*. have used isothioureas to catalyse intra- and inter-molecular Michael addition-lactonisation reactions (Scheme 23).[70] It was found that tetramisole (**129**) catalysed the intramolecular Michal addition-lactonisation sequence of a range of enone-acids (**127**) to form carbo- and hetero-cyclic lactones (**128**) in high yield with excellent levels of diastereoselectivity and ee (Scheme 23a). The lactone products (**128**) could be ring-opened using either methanol or isopropylamine to form the corresponding indene or dihydrobenzofuran carboxylates. Further optimisation allowed the process to be extended to the intramolecular reaction between arylacetic acids (**130**) and α-keto-β,γ-unsaturated esters (**131**) (Scheme 23b). In this case, HBTM derivative **41** was found to be the best catalyst, providing *anti*-dihydropyranones (**132**) in high de and ee. The intra- and inter-molecular reactions are thought to proceed *via* similar stepwise Michael addition-lactonisation mechanisms. Firstly, the pivaloyl chloride reacts with the acid present to form a mixed anhydride, which can then be nucleophilically attacked by the isothiourea catalyst to form an *N*-acyl intermediate. The $^{i}Pr_2NEt$ present can then deprotonate the *N*-acyl intermediate to form a zwitterionic species (**133**) that then undergoes a Michael addition onto the α,β-unsaturated ketone (Scheme 23c). Subsequent lactonisation of the enolate formed (**134**) gives the lactone product and releases the catalyst. This proposed mechanism also provides an explanation for the absolute stereochemistry observed by assuming that the Michael addition proceeds with the two pro-stereocentres adopting a staggered conformation to minimise unfavourable non-bonding interactions.



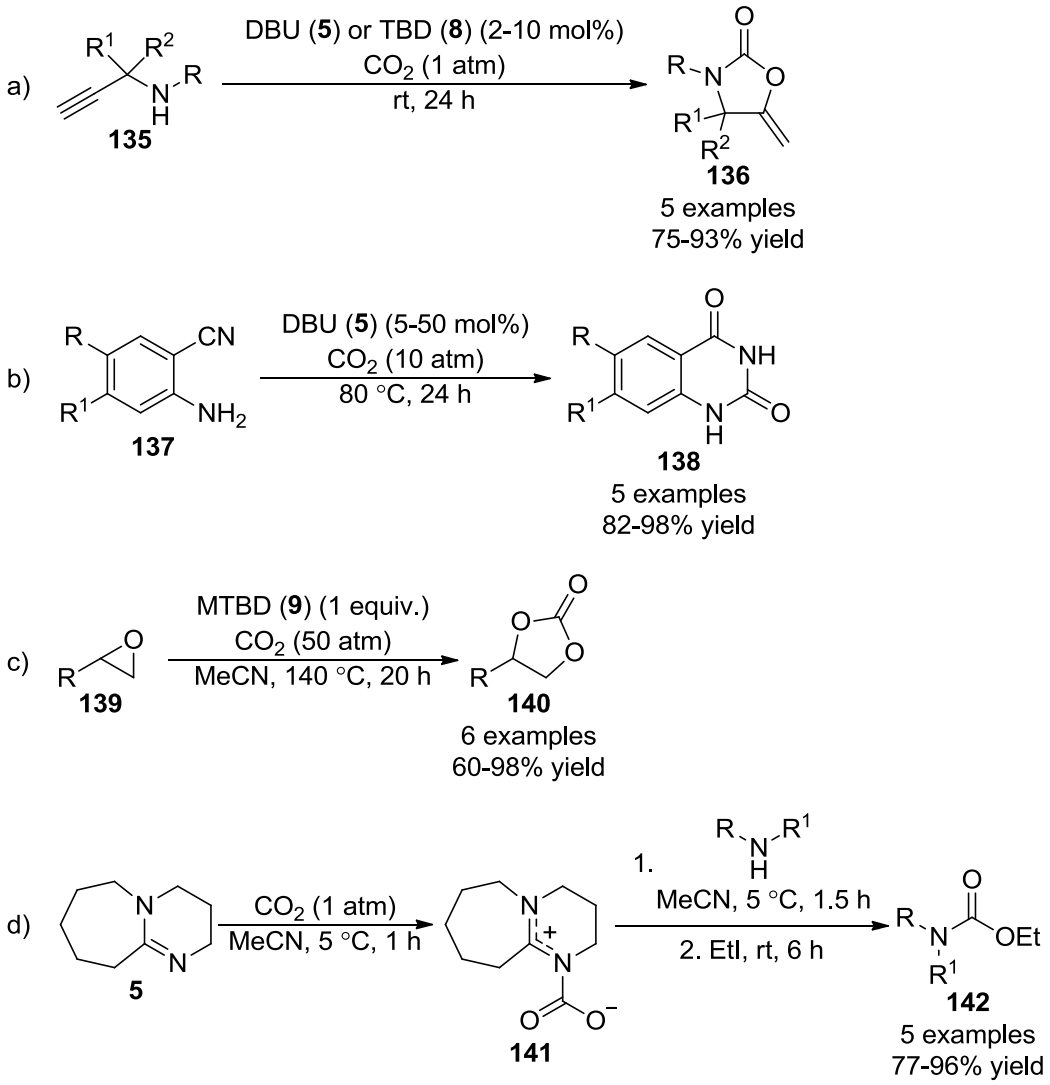
Scheme 23. a) Intramolecular Michael addition-lactonisation reaction. b) Intermolecular Michael-addition-lactonisation reaction. c) Proposed intermediates in the isothiourea **41** catalysed process.[70]

A number of guanidine catalysed conjugate additions have been reported over the last 15 years. However, whilst nucleophilic catalysis is theoretically possible, most reports favour either general Brønsted base catalysis or hydrogen-bonding models to explain the role of the guanidine catalyst.[71-77]

1.3.5 Carbonylation Reactions

In 1996, Costa and co-workers showed that both DBU (**5**) and TBD (**8**) catalyse the reaction of acetylinic amines (**135**) with CO_2 to form 5-methylene-oxazolidin-2-ones (**136**) (Scheme 24a). Although no mechanism was proposed for the role of the amidine or guanidine catalysts it was found that the rate of reaction was independent of the pK_a of the catalyst.[78] Mizuno *et al*. then found that DBU (**5**) could catalyse the reaction between CO_2 and 2-aminobenzonitriles (**137**). The reaction readily occurs in one atmosphere of CO_2 if one equivalent of DBU (**5**) is used,[79] whereas the use of sub-stoichiometric amounts of DBU (**5**) required ten atmospheres of CO_2 (Scheme 24b).[80] Sartori *et al*. reported that the guanidine MTDB (**9**) catalyses the cycloaddition

of CO_2 to epoxides (**139**) to form cyclic carbonates (**140**) (Scheme 24c). Franco and co-workers were the first to suggest that CO_2 is nucleophilically activated by the amidine or guanidine catalysts when they showed that a DBU-CO_2 complex (**141**) reacts with amines.[81] The initial addition products were trapped with ethyl iodide to form the corresponding ethyl carbamates (**142**) in high yields (Scheme 24d). The structure of the DBU-CO_2 complex (**141**) was subsequently analysed by ^{13}C NMR spectroscopy, although attempts to obtain an X-ray crystal structure resulted in the formation of a DBU-carbonic acid complex during the crystallisation process.[82]

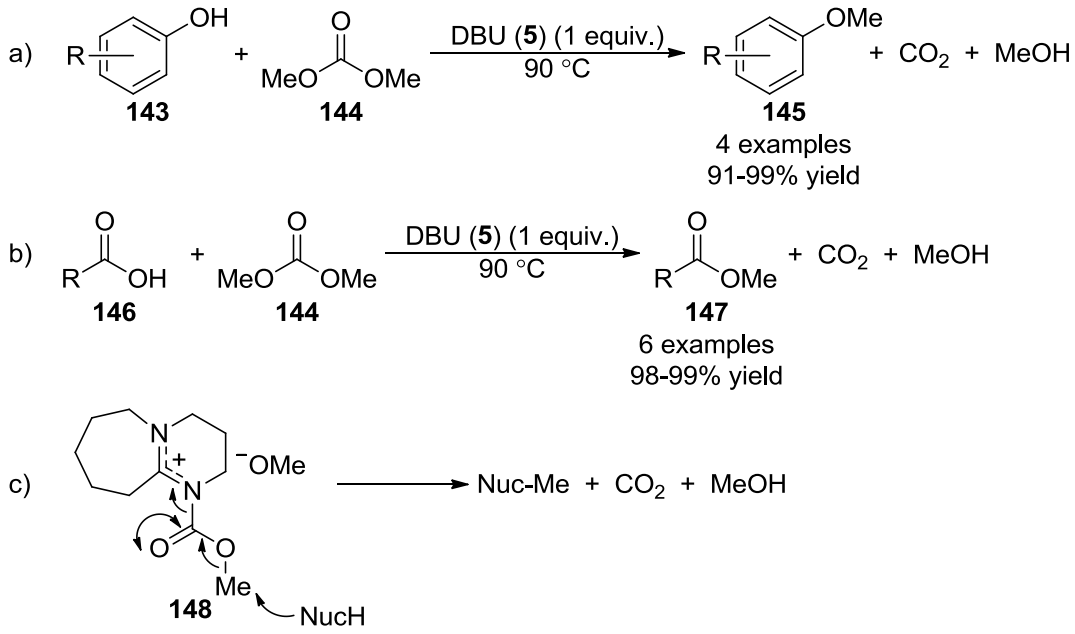


Scheme 24. Examples of the nucleophilic activation of CO_2 using amidine and guanidine based catalysts.[78-82]

1.3.6 Methylation Reactions

In 1990, Sennyey *et al*. found that tetrasubstituted guanidines could be used to catalyse the methylation of phenols (**143**) using dimethyl carbonate (**144**) at high temperature (180 °C).[83]

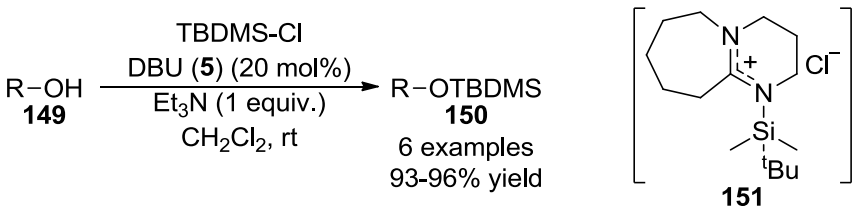
Shieh *et al*. subsequently found that using one equivalent of DBU (**5**) was more efficient, allowing the methylation of phenols (**143**) to occur at 90 °C (Scheme 25a).[84] Shieh *et al*. also found that DBU (**5**) and dimethyl carbonate (**144**) could be used for the methylation of acids (**146**) to form the corresponding esters (**147**) (Scheme 25b).[85] Extensive mechanistic studies have shown that DBU (**5**) and dimethyl carbonate (**144**) react to form an *N*-acyl carbamate (**148**), which acts as the methylating agent towards nucleophiles, releasing CO_2 and methanol as by-products (Scheme 25c).



Scheme 25. DBU (**5**) and dimethyl carbonate (**144**) for the *O*-methylation of a) phenols (**143**) and b) acids (**146**). c) Proposed mechanism.[84-85]

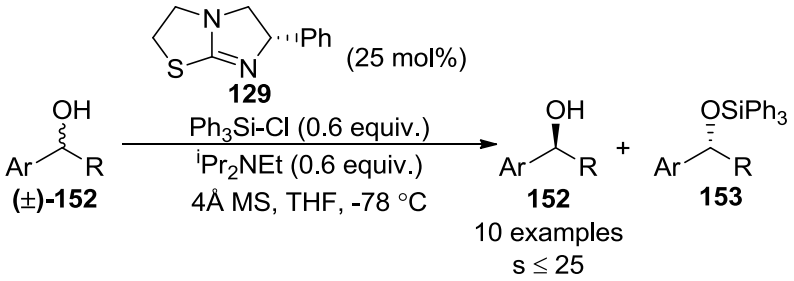
1.3.7 Silylation Reactions

In 1985, Kim and Chang showed that DBU (**5**) could be used as a nucleophilic catalyst in the *tert*-butyldimethylsilylation of primary alcohols (**149**) (Scheme 26).[86] The silylation reaction can be performed using either one equivalent of DBU (**5**) or 20 mol% DBU (**5**) and one equivalent of triethylamine, providing protected products (**150**) in high yields. The silylation methodology was shown to be regioselective for the protection of primary alcohols over secondary alcohols. The DBU (**5**) is believed to attack the TBDMS-Cl to form an *N*-TBDMS DBU complex **151**, which then acts as the silylating agent.



Scheme 26. Silylation of primary alcohols (**149**) catalysed by DBU (**5**).[86]

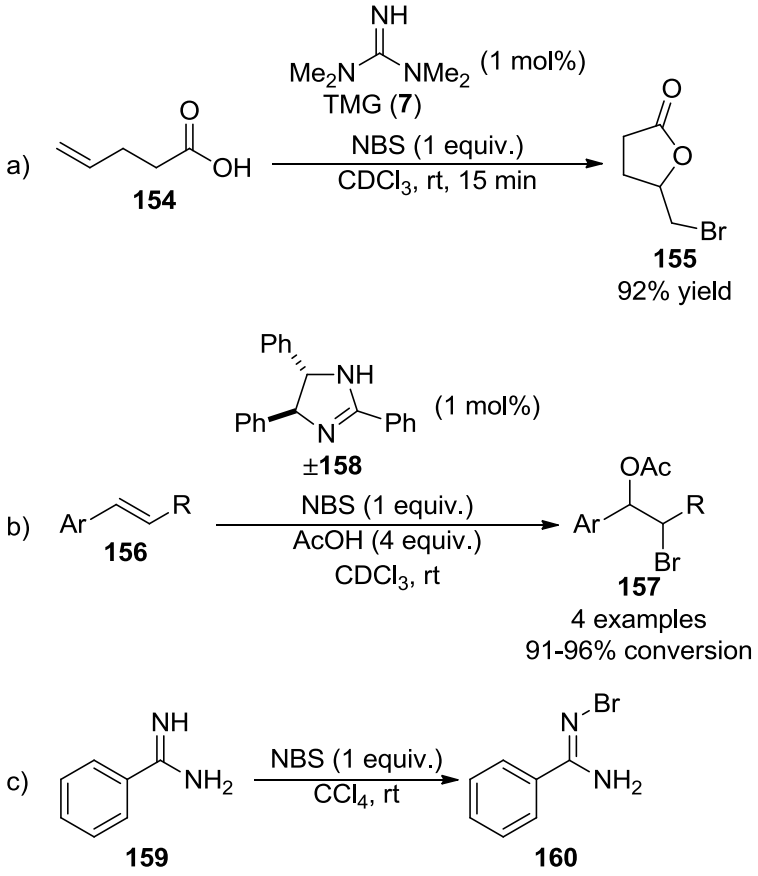
Recently, Wiskur *et al*. have used the enantiomerically pure tetramisole (**129**) as a nucleophilic catalyst for the kinetic resolution of secondary alcohols (**152**) through enantioselective silylation (Scheme 27).[87] The highest enantioselectivities were observed using cyclic secondary alcohols (**152**) and triphenylsilyl chloride, giving *s* values of up to 25 that corresponded to an 88% ee for recovered alcohol at 52% conversion (**152**).



Scheme 27. Kinetic resolution of secondary alcohols (**152**) through enantioselective silylation catalysed by tetramisole (**129**).[87]

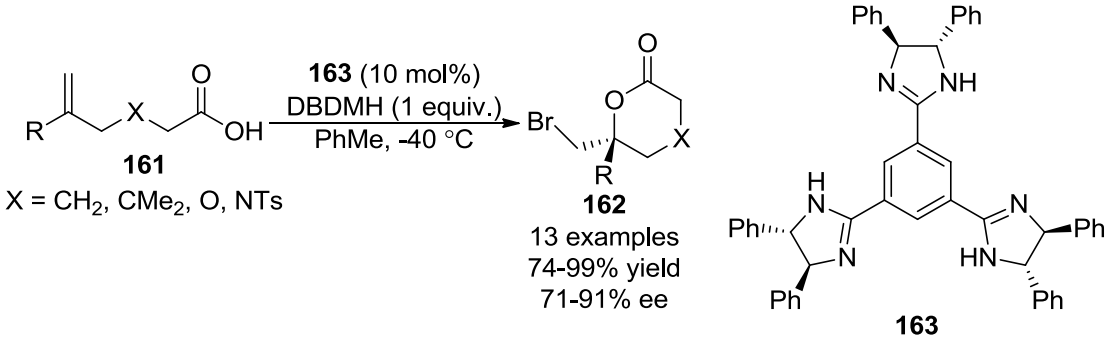
1.3.8 Bromination Reactions

Braddock and co-workers have found that amidine and guanidines can be used as nucleophilic catalysts in bromination reactions. Firstly, the acyclic guanidine TMG (**8**) was shown to be a highly efficient catalyst for bromolactonisation and intermolecular bromoacetoxylation using *N*-bromosuccinimide (NBS). For example, the uncatalysed reaction of 4-pentenoic acid (**154**) with NBS forms 15% of bromolactone **155** in 15 hours, whereas adding 1 mol% TMG (**8**) gives a 92% isolated yield after only 15 minutes (Scheme 28a).[88] The cyclic amidine (±)-*iso*-amarine (**158**) was also shown to catalyse the same reactions using NBS. The bromoacetoxylation of styrenes (**156**) was found to be highly regioselective for attack of acetic acid at the benzylic position of the bromonium ion (Scheme 28b).[89] The amidine and guanidine catalysts are thought to provide a more electrophilic source of bromine by nucleophilically attacking NBS. An X-ray crystal structure of *N*-bromo-benzamidine (**160**), obtained from the reaction of benzamidine (**159**) with one equivalent of NBS, provides direct evidence for this mode of activation by amidines.



Scheme 28. a) Bromolactonisation catalysed by TMG (**8**).[88] b) Bromoacetoxylation catalysed by (±)-*iso*-amarine (**158**). c) Evidence for the activation of NBS by amidines.[89]

Recently, Fujioka *et al*. have shown that the C_3-symmetric amidine derivative **163** can catalyse the asymmetric bromolactonisation of a range of δ,ε-unsaturated acids (**161**) using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), forming the corresponding bromolactones (**162**) in high yields with good levels of enantioselectivity (Scheme 29).[90] In this case, the formation of an ion-



Scheme 29. Asymmetric bromolactonisation reaction catalysed by a C_3-symmetric amidine **163**.[90]

pair between the acid (**161**) and the catalyst (**163**) is thought to be important for asymmetric induction and it is unknown if the catalyst (**163**) nucleophilically activates the electrophilic bromine source.

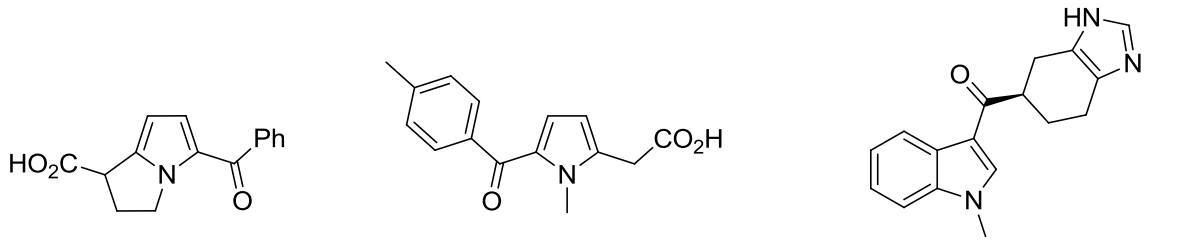
1.4 Conclusions

Amidines, guanidines, and isothioureas have been shown to act as nucleophilic catalysts in a wide range of reactions. In particular, the bicyclic amidines DBU (**5**) and DBN (**6**) and the guanidines TMG (**7**) and TBD (**8**) have proven to be highly active nucleophilic catalysts in many cases, often offering advantages over other more traditional nucleophilic catalyst. Enantiomerically pure derivatives of amidines, guanidines and, in particular, isothioureas have been successfully used in a number of asymmetric reactions. The potential of the amidine and guanidine functional groups to act as bifunctional catalysts, using combinations of nucleophilic, basic, and hydrogen-bonding behaviour, has been exploited in a few processes. There is no doubt that further applications of amidine, guanidine, and isothiourea derived catalysts will continue to be discovered.

2 Organocatalytic Friedel-Crafts Acylation of Pyrroles and Indoles

2.1 Introduction

Substituted pyrroles and indoles are found in many natural products and biologically active compounds (Figure 4).[91] However, their synthesis remains challenging, with syntheses often suffering from poor regioselectivity and/or low yields due to oxidative degradation.[92] Lewis acid catalysed Friedel-Crafts acylation is one of the most versatile and powerful methods of preparing aromatic ketones,[93] however, protocols for the synthesis of heteroaromatic ketones are less well established. The difficulties involved in the synthesis and purification of pyrroles may help explain why a limited number have been incorporated as fragments into drug molecule targets when compared with the widespread popularity of indoles and imidazoles as pharmaceutical targets. However, due to their less restricted patent position, functionalised pyrroles are likely to become increasingly important targets as scaffolds for drug discovery purposes. In view of the great potential of acylated pyrroles and indoles for the synthesis of medicinally active compounds,[94] an organocatalytic methodology for the Friedel-Crafts acylation of heteroaromatic compounds was investigated.



(±)-Ketorolac (**164**) Tolmetin (**165**) Ramosetron (**166**)

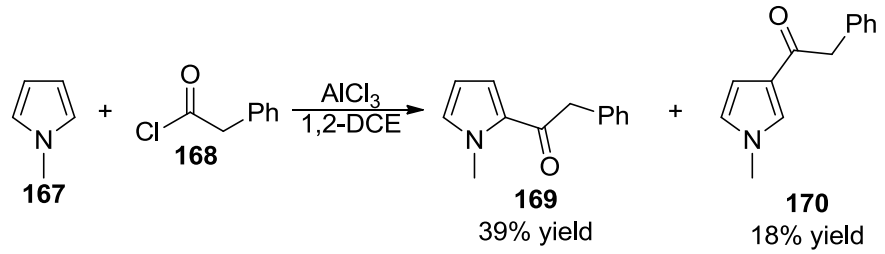
non-steroidal anti-inflammatory drugs *serotonin receptor antagonist*

Figure 4. Examples of biologically active acyl pyrroles and indoles.

2.1.1 Lewis Acid Catalysed Friedel-Crafts Acylation of Pyrroles and Indoles

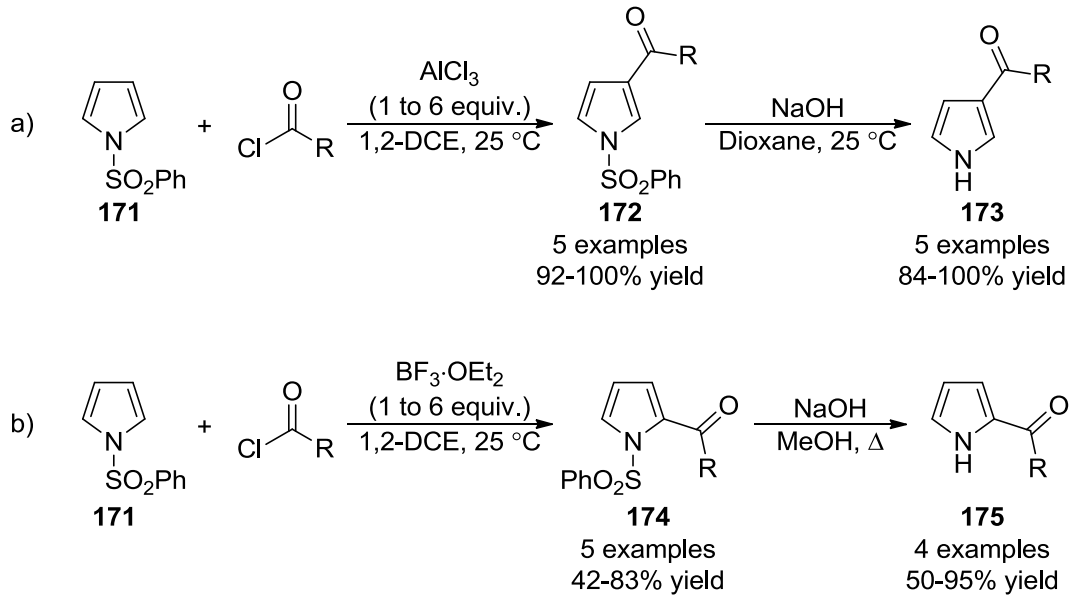
Traditionally, stoichiometric amounts of Lewis acids have been used for the acylation of pyrroles and other heteroaromatic compounds. Other methods, including the Vilsmeier-Haack reaction, thermal rearrangement of *N*-acyl pyrroles, and additions of pyrrolmagnesium halides to acyl chlorides or 2-pyridylthioesters, have also been used to form *C*2- and *C*3-acyl pyrroles, but the Lewis acid catalysed Friedel-Crafts reaction still remains the most commonly used method.[95]

However, the Lewis acid catalysed acylation of heteroaromatic compounds is challenging as reactions can suffer from poor regioselectivity, whilst the reactants and substrates are prone to acid catalysed polymerisation and oxidative degradation leading to low yields of acylated products. For example, Massa and co-workers reported that the traditional Friedel-Crafts acylation of *N*-methylpyrrole (**167**) with 2-phenylacetyl chloride (**168**) using a stoichiometric amount of $AlCl_3$ gives a mixture of *C*2- and *C*3-regioisomers of acyl pyrrole (**169** and **170**) in a low yield (Scheme 30).[96]



Scheme 30. The $AlCl_3$ catalysed Friedel-Crafts acylation of *N*-methylpyrrole (**167**) gives a mixture of regioisomers in low yields.[96]

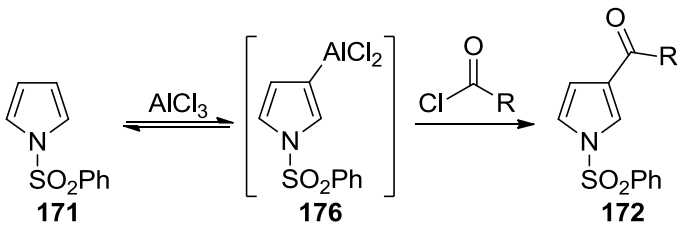
Katushima and co-workers developed one of the first practical methods for regioselectively acylating pyrroles by acylating *N*-phenylsulfonyl protected pyrrole (**171**) with acyl chlorides at either its *C*2 or *C*3 position, depending on the Lewis acid catalyst used. The use of stoichiometric amounts of $AlCl_3$ resulted in selective *C*3 acylation (Scheme 31a), whilst the *C*2 acyl pyrrole (**174**) could be obtained by using the milder Lewis acid $BF_3{\cdot}OEt_2$ as a catalyst



Scheme 31. The regioselectivity of the acylation of *N*-(phenylsulfonyl)pyrrole (**171**) is dependent on the Lewis acid catalyst.[97-98]

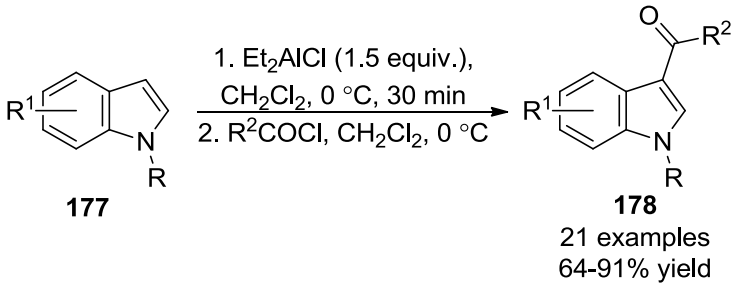
(Scheme 31b). In both cases, the phenylsulfonyl protecting group could be removed *via* base hydrolysis to provide the free acyl pyrrole (**173** and **175**).[97-98] This methodology was subsequently applied to the acylation of indoles, with *N*-(phenylsulfonyl)indole being acylated in its *C*3 position using $AlCl_3$ as a stoichiometric catalyst.[99]

Katushima *et al*. proposed that the effect of Lewis acid strength on the regioselectivity of acylation of pyrrole was due to the formation of a highly polarised acyl chloride-$AlCl_3$ species that reacts selectively at the *C*3-position under charge control, whilst a less-polarised acyl chloride-$BF_3{\cdot}OEt_2$ species reacts under orbital control at the *C*2-position.[98] However, detailed experimental evidence by Huffman *et al.*, published twenty-five years after Katushima's seminal work, suggested that the acylation of *N*-(phenylsulfonyl)pyrrole (**171**) with $AlCl_3$ proceeds *via* reaction of a *C*3-organoaluminium intermediate (**176**) with the acyl chloride (Scheme 32). Acylations using milder Lewis acids proceed *via* a traditional Friedel-Crafts reaction, with the *N*-(phenylsulfonyl)pyrrole (**171**) reacting with a polarised acyl chloride-Lewis acid complex in the favoured *C*2-position.[100]



Scheme 32. Proposed *C*3-organoaluminium intermediate (**176**) in the acylation of *N*-(phenylsulfonyl)pyrrole (**171**) using $AlCl_3$.[100]

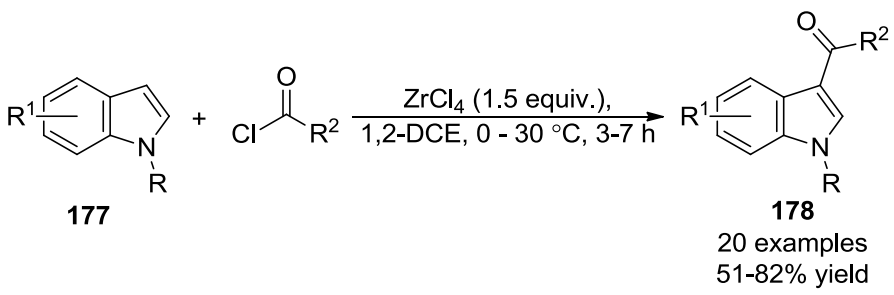
Since the breakthrough of Katushima and co-workers, a number of variations of the aluminium promoted acylation of pyrrole and indoles have been reported. Okauchi *et al*. found that substituted indoles (**177**) could be acylated with a range of acyl chlorides using 1.5 equivalents of diethylaluminium chloride (Scheme 33). The reaction presumably proceeds through the formation of a *C*3-organoaluminium complex as the substituted indole and Et_2AlCl are stirred for 30 minutes before the acyl chloride is added.[101] Ottoni and co-workers reported a similar procedure for the selective *C*3-acylation of unsubstituted indole with acyl chlorides using $SnCl_4$ as a stoichiometric Lewis acid catalyst. The pre-formation of the *C*3-organotin species, by reacting $SnCl_4$ with indole before adding the acyl chloride, prevented unwanted side reactions such as *N*-acylation and polymerisation of indole that are often seen with other Lewis acids.[102]



Scheme 33. Selective *C*3-acylation of indoles (**177**) using Et_2AlCl as a Lewis acid.[101]

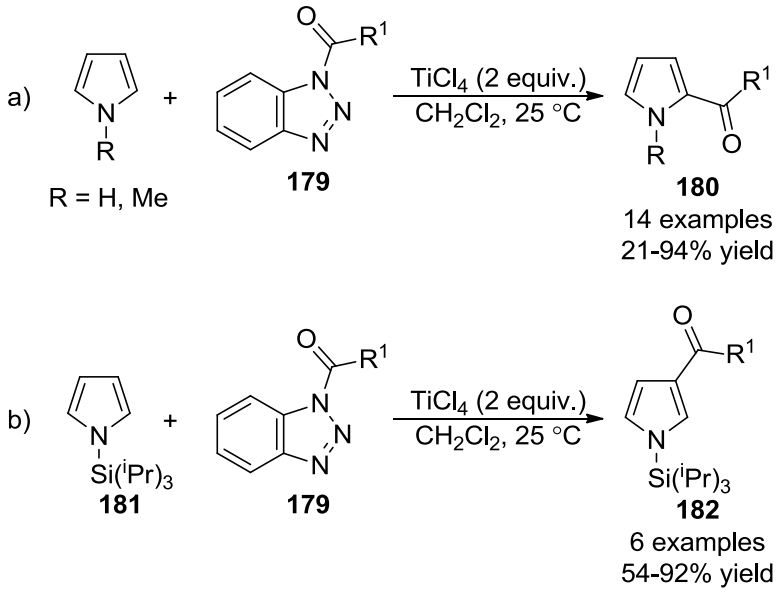
Yeung *et al*. have used an acidic imidazolium chloroaluminate ionic liquid, generated from 1-ethyl-3-methylimidazolium chloride and $AlCl_3$, to promote the *C*3-acylation of unprotected indoles with acyl chlorides at room temperature. However, this methodology is limited as less reactive acyl chlorides and electron-rich indoles predominately form indole dimerisation products in favour of the desired acyl indole.[103] Kantam *et al*. and Álvaro *et al*. have both used forms of aluminium based beta zeolite to promote the acylation of pyrrole and indole with acetic anhydride. However, the reactions are low yielding and give poor *C*2/*C*3 regioselectivity in the acylation of pyrrole.[104-105]

There are also a number of reports of other metals being used as stoichiometric Lewis acid catalysts for the acylation of heteroaromatic compounds. For example, Yadav and co-workers have used two equivalents of zinc metal to promote the *C*2-acylation and *C*2-sulfonylation of both unprotected and *N*-protected pyrrole with acyl chlorides at room temperature in toluene. The reaction works for a range of aromatic, heteroaromatic, and alkyl acyl chlorides, providing the *C*2-acylated pyrroles in high isolated yields.[95] Recently, Guchhait *et al*. have reported a regioselective reaction for the *C*3-acylation of a number of indoles (**177**) with a range of acyl chlorides using 1.5 equivalents of $ZrCl_4$ as a catalyst (Scheme 34). Although the reaction works for an impressive range of substrates, the experimental procedure is more complex than other reported methods and requires the use of an inert atmosphere of nitrogen.[106]



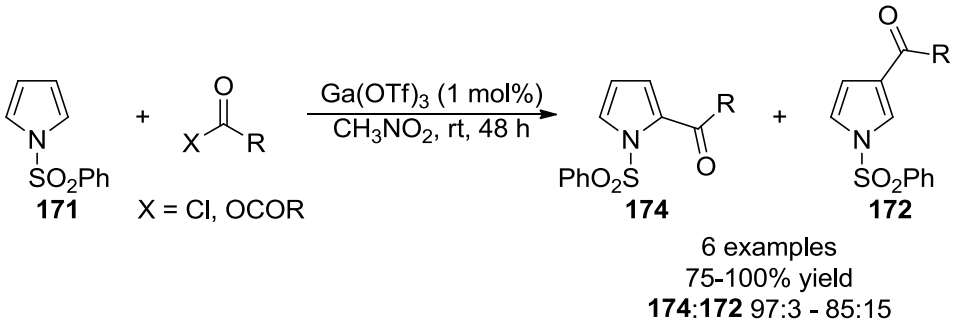
Scheme 34. $ZrCl_4$ promoted Friedel-Crafts acylation of indoles.[106]

Katritzky *et al*. have developed a method of regioselectively acylating pyrroles using *N*-acylbenzotriazoles (**179**) as the acyl source and two equivalents of $TiCl_4$ as a Lewis acid. Pyrrole and *N*-methylpyrrole (**167**) were regioselectively acylated at the *C*2-position (Scheme 35a), whilst introduction of a bulky triisopropylsilyl (TIPS) group on the pyrrole nitrogen gave selective *C*3-acylation under the same conditions (Scheme 35b). This methodology can also be applied to the *C*3-acylation of indole and *N*-methylindole. The enhanced stability of *N*-acylbenzotriazoles (**179**) compared with acyl chlorides allowed a number of heteroaromatic acyl-pyrroles and acyl-indoles to be synthesised in good yield that are not available by other methods.[107]



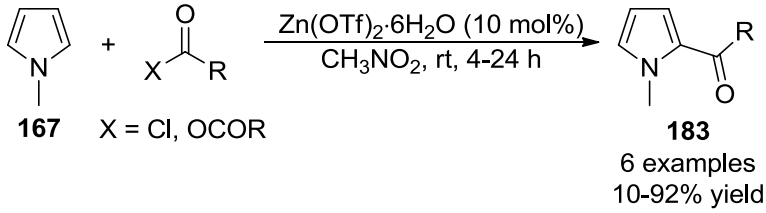
Scheme 35. Regioselective acylation of pyrroles using *N*-acylbenzotriazoles (**179**) as the acyl source.[107]

Whilst all of the above methods use stoichiometric amounts of Lewis acids to promote the acylation of pyrroles and indoles, there are a few reports on metal-based catalytic methods of acylating heteroaromatics, with metal triflate catalysts being the most successful to date.[108-110] For example, Kobayashi *et al*. have shown that $Ga(OTf)_3$ and related metal triflates catalyse the *C*2-acylation of *N*-(phenylsulfonyl)pyrrole (**171**) with acyl chlorides and acid anhydrides in good yields, although competing formation of the *C*3-regioisomer (**172**) was observed in many cases (Scheme 36). This catalytic system can also be applied to the acylation of other heteroaromatic compounds such as furan, benzofuran, and thiophene, which are much less reactive towards acylation than pyrrole.[108]



Scheme 36. $Ga(OTf)_3$ catalysed acylation of *N*-(phenylsulfonyl)pyrrole (**171**).[108]

Su *et al*. have demonstrated that $Zn(OTf)_2 \cdot 6H_2O$ is an efficient catalyst for the acylation of *N*-methylpyrrole (**167**), furan, and thiophene, using a limited range of acyl chlorides and acetic anhydride. In this case, the reaction is completely *C*2-regioselective and provides the acylated products in reasonable yields, although straight chain and heteroaromatic acyl chlorides required longer reaction times and gave acylated products (**183**) in reduced yields (Scheme 37).[110] Recently, Boroujeni has reported that polystyrene supported $Al(OTf)_3$ can catalyse the regioselective Friedel-Crafts acylation of a number of aromatic compounds including pyrrole, furan, thiophene, and indole with benzoyl or acetyl chloride.[111]



Scheme 37. Regioselective $Zn(OTf)_2 \cdot 6H_2O$ catalysed acylation of *N*-methylpyrrole.[110]

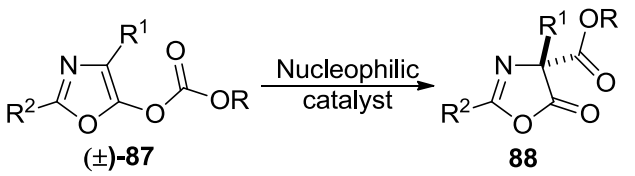
All previous methods for the *C*-acylation of pyrroles and indoles employ either stoichiometric amounts of Lewis acid or use transition metal based catalysts, both of which have environmental and toxicity problems associated with their use. An organocatalytic method for the *C*-acylation of heteroaromatic compounds would therefore provide a valuable alternative to current methods and could have potential applications in the synthesis of drug molecules.

2.1.2 Organocatalytic *C*-Acylations

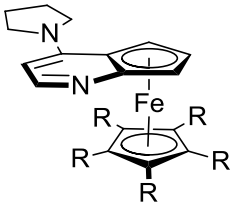
Organocatalysts have been used extensively for the *O*-acylation of alcohols and the *N*-acylation of amines,[11,112] but there are few examples of organocatalytic *C*-acylations. Most success has been achieved in intramolecular *O*- to *C*-acyl transfer reactions using nucleophilic organocatalysts, which can allow the formation of quaternary carbon centres. Steglich and Höfel

were the first to show that both DMAP (**39**) and 4-(pyrrolidino)pyridine (PPY) could be used to catalyse the *O*- to *C*-acyl transfer rearrangement of 5-oxazole carbonate derivatives (**87**) to their corresponding 4-carboxyazlactones (**88**) and, as such, this is often referred to as the Steglich rearrangement.[113] Black and co-workers then showed that enol carbonates of 3-phenylbenzofuranone could also be rearranged to their 3-acyl derivatives using DMAP (**39**) as a catalyst.[114]

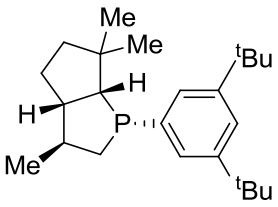
Since these initial reports, a number of enantiomerically pure organocatalysts have been developed for the intramolecular asymmetric *O*- to *C*-acyl transfer reactions of 5-oxazole carbonates (**87**), which are summarised in Scheme 38.[115-116] Fu and Ruble were the first to report an enantioselective version of this reaction, using a planar chiral PPY derivative (**184**) to promote the rearrangement of a number of substituted oxazolyl carbonates (**87**), forming azlactone products (**88**) in high yields with high ee.[117-118] Vedejs *et al*. developed an enantiomerically pure phosphine as a catalyst (**186**) for the same reaction and subsequently improved the yields and ee of product obtained using an enantiomerically pure DMAP derivative (**187**) as a catalyst.[119] Gotor and co-workers synthesised a simpler DMAP derivative (**189**) for the rearrangement, but the ee of the azlactone products (**88**) obtained were lower than for Vedejs' DMAP catalyst (**187**).[120] Richards *et al*. have synthesised a planar chiral cobaltocene derivative (**188**) in three steps from (*S*,*S*)-hexane-2,5-diol to catalyse the rearrangement. Whilst complex **188** showed good catalytic activity, the ee of the products from the rearrangement were inferior to those reported by Fu for his planar chiral PPY derivative (**184**).[121] Smith *et al*. initially showed that an achiral DHPB (**42**) efficiently catalysed the *O*- to *C*-acyl transfer reaction of oxazolyl carbonates (**87**),[52] before going on to develop an enantiomerically pure DHPB derivative (**41**) that formed the azlactone products (**88**) in good yields and with excellent ee.[54] Smith *et al*. have also shown that both achiral and enantiomerically pure *N*-heterocyclic carbenes efficiently catalyse the rearrangement, but the latter give poor levels of ee compared with the isothiourea catalyst (**41**).[122-124] Gröger and co-workers also used an isothiourea (**76**) to catalyse the rearrangement, but their BTM (**76**) catalyst gave lower levels of ee compared with Smith *et al*.'s DHPB derivative (**41**).[53] Zhang *et al*. have designed a bicyclic imidazole catalyst **191** that efficiently catalyses the rearrangement reaction, forming the products in good yields with high ee.[125] Recently, Ooi *et al*. have applied a completely different type of catalyst to the *O*- to *C*-acyl transfer reaction, using a chiral ammonium betaine (**190**) as an ionic nucleophilic catalyst to form a number of azlactones (**88**) in excellent yields with excellent levels of ee.[126]



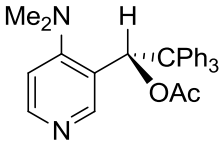
(±)-**87** **88**



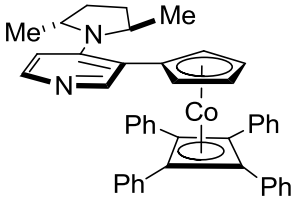
R = Me (**184**), R = Ph (**185**)
Fu (1998)[117-118]
up to 90% ee



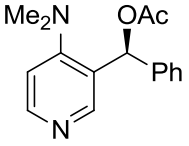
186
Vedejs (2003)[119]
up to 92% ee



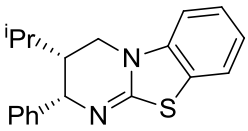
187
Vedejs (2003)[119]
up to 95% ee



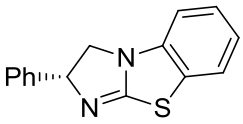
188
Richards (2006)[121]
up to 76% ee



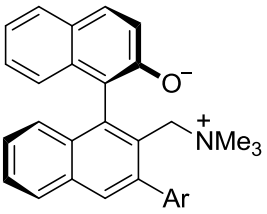
189
Gotor (2006)[120]
up to 70% ee



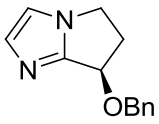
41
Smith (2009)[54]
up to 94% ee



76
Gröger (2009)[53]
up to 61% ee



Ar = 3,5-$(CF_3)_2C_6H_3$
190
Ooi (2010)[126]
up to 97% ee

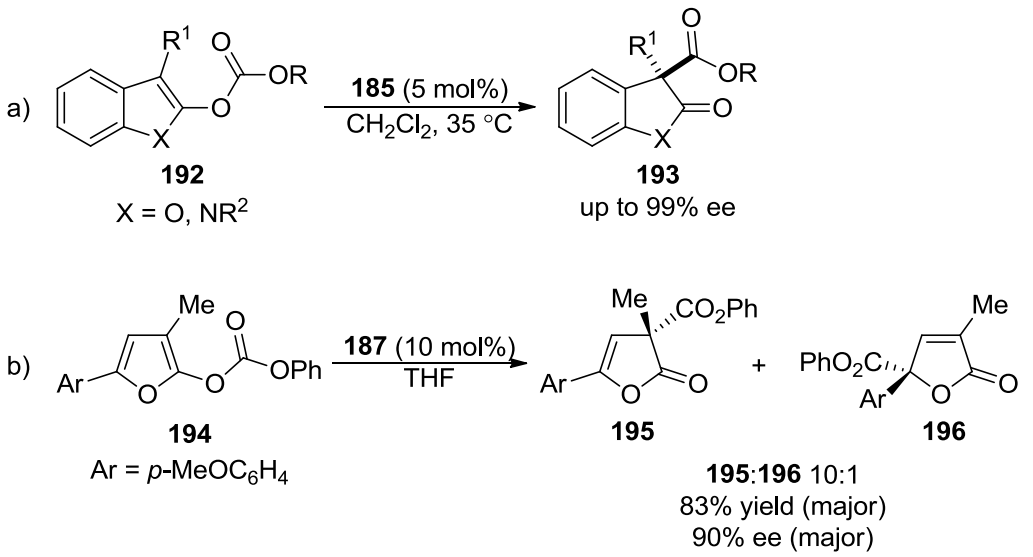


191
Zhang (2010)[125]
up to 95% ee

Scheme 38. Enantiomerically pure catalysts used for the stereoselective *O*- to *C*-acyl transfer of 5-oxazole carbonates (**87**) to their corresponding 4-carboxyazlactones (**88**).

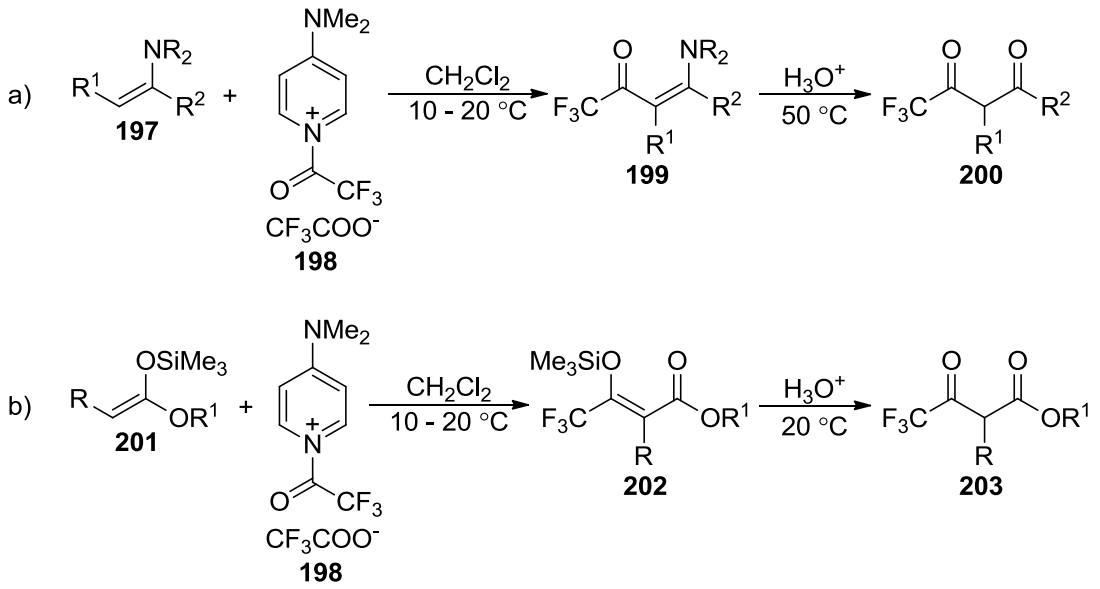
A number of the catalysts shown in Scheme 38 have subsequently been applied to the intramolecular *O*- to *C*-acyl transfer reactions of other substrates. For example, Fu and Hills have applied the planar chiral PPY catalyst **185** to the enantioselective synthesis of oxindoles (**193**, X = NR^2) and benzofuranones (**193**, X = O) through rearrangement of the corresponding *O*-acyl derivatives (**192**) (Scheme 39a).[127] Richards *et al*. also applied their planar chiral cobaltocene DMAP catalyst (**188**) to the rearrangement of oxindole enol carbonates (**192**) but, as seen previously, the ee of the products are lower than those observed using Fu's catalyst.[128] Vedejs *et al*. used their enantiomerically pure DMAP derivative **187** to catalyse the

intramolecular rearrangement of furanyl (**194**), benzofuranyl, and oxindole (**192**, X = NR^2) enol carbonates. The rearrangement of furanyl enol carbonates (**194**) gave a mixture of regioisomers of lactone products (**195** and **196**), although the major regioisomer of product was isolated with high levels of ee in most cases (Scheme 39b).[129] Smith *et al*. also obtained a mixture of lactone regioisomers when they applied their isothiourea catalyst **41** to the rearrangement of furanyl enol carbonates (**194**), again observing good levels of ee for the major isomer of lactone product (**195**).[55]



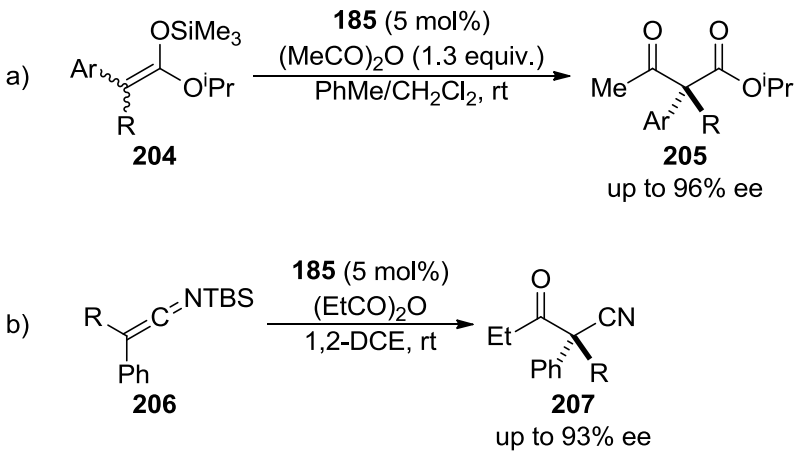
Scheme 39. Application of the intramolecular *O*- to *C*-acyl transfer reactions to a) oxindol enol carbonates and benzofuranone enol carbonates (**192**) and b) furanyl enol carbonates (**194**).[127,129]

Whilst there are a number of reports on organocatalytic intramolecular *C*-acylations, there are far fewer on organocatalytic intermolecular *C*-acylations. This is due to the fact that reactions with nucleophiles such as enolates and enol ethers often undergo preferential *O*-acylation over *C*-acylation. The first indication that an organocatalytic *C*-acylation reaction might be possible came from Simchen and Schmidt, who showed that both enamines (**197**) and silyl ketene acetals (**201**) could be chemoselectively *C*-acylated using stoichiometric amounts of an *N*-trifluoroacetyl-DMAP salt (**198**). The resulting *C*-acyl enamines (**199**) and silyl enol ethers (**202**) could be readily hydrolysed to give 1,3-diketones (**200**) and β-keto esters (**203**) respectively (Scheme 40a and b).[130]



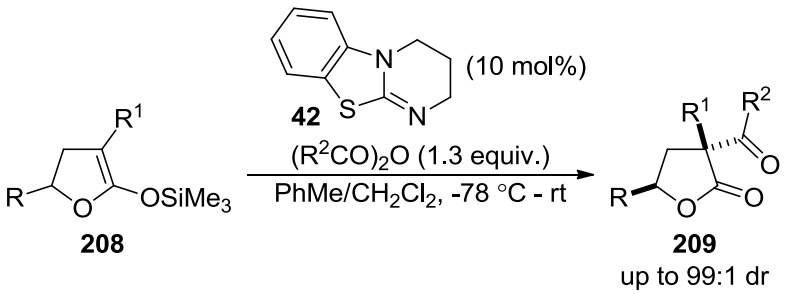
Scheme 40. Intermolecular *C*-acylations of a) enamines (**197**) and b) silyl ketene acetals (**201**) using a stoichiometric *N*-trifluoroacetyl-DMAP salt (**198**).[130]

The first organocatalytic intermolecular *C*-acylation reactions were reported by Fu and Mermerian, who used the planar chiral PPY catalyst **185** to enantioselectively acylate a number of silyl ketene acetals (**204**) with acetic anhydride to form β-keto esters (**205**) containing all-carbon quaternary stereocentres. Initially the reaction was reported for a series of cyclic silyl ketene acetals,[131] but the scope was later expanded to a number of acyclic silyl ketene acetals (**204**). It was found that the *E*/*Z* geometry of the silyl ketene acetal (**204**) was unimportant, with both isomers reacting to give the same enantiomer of product (**205**) (Scheme 41a). Mechanistic studies showed that the reaction proceeds *via* activation of both the anhydride, through formation of an *N*-acyl-pyridinium species with the catalyst, and the silyl ketene acetal, through generation of an enolate by reaction with an acetate anion.[132] Fu and Mermerian subsequently reported that catalyst **185** also promotes the reaction of silyl ketene imines (**206**) with propanoic anhydride, forming α-cyano carbonyl compounds (**207**) containing quaternary stereocentres with good ee (Scheme 41b).[133]



Scheme 41. Organocatalytic intermolecular *C*-acylations of a) silyl ketene acetals (**204**) and b) silyl ketene imines (**206**) using a planar chiral PPY derivative (**185**).[131-133]

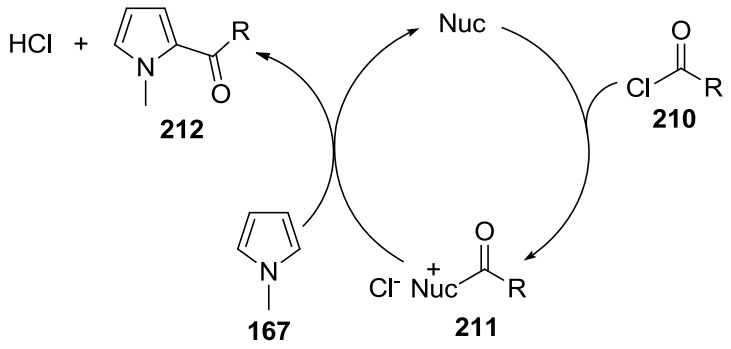
More recently, Smith and co-workers have shown that DHPB (**42**) catalyses the intermolecular *C*-acylation of a number of cyclic silyl ketene acetals (**208**) with a range of simple anhydrides. The reaction generates cyclic β-keto esters (**209**) containing a chiral quaternary carbon and was shown to be highly diastereoselective in all cases (Scheme 42).[57]



Scheme 42. Isothiourea (**42**) catalysed diastereoselective intermolecular *C*-acylation of cyclic silyl ketene acetals (**208**).[57]

2.1.3 Organocatalytic Friedel-Crafts Acylation

Whilst there are a few examples of intramolecular organocatalytic *C*-acylations of silyl ketene acetals and related compounds, there are currently no Lewis acid free variations of the Friedel-Crafts reaction for the acylation of heteroaromatic substrates. It was thought that the electrophilicity of acyl chlorides (**210**) towards heteroaromatics, such as *N*-methylpyrrole (**167**), could be increased sufficiently by activation using a nucleophilic catalyst. This would allow intermolecular *C*-acylation to occur through attack of the activated intermediate (**211**) by the heteroaromatic substrate, releasing the *C*-acylated product (**212**) whilst regenerating the catalyst to continue in the cycle (Scheme 43).



Scheme 43. Proposed organocatalytic Friedel-Crafts acylation of *N*-methylpyrrole (**167**).

2.2 Results and Discussion

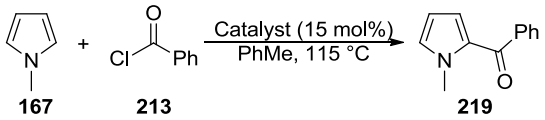
Initially, a range of organocatalysts for the acylation of commercially available *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) was screened, as summarized in Table 2. The reactions were performed in nitrogen purged carousel tubes using 1 mmol of *N*-methylpyrrole (**167**), 1.2 mmol of benzoyl chloride (**213**), and 15 mol% of the appropriate catalyst in 1 mmol of toluene at reflux for 1.5 hours.[†] Conversions into acylated products were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures using 2,5-dimethylfuran as an internal standard.[134] The regioselectivity of the reaction was also determined by analysis of signals from the pyrrole ring-protons in the crude ^{1}H NMR spectra. The ^{1}H NMR spectrum of 2-benzoyl-*N*-methylpyrrole (**219**) has three distinct signals, each integrating to one proton, between δ = 6 and 7 ppm, whereas the ^{1}H NMR spectrum of 3-benzoyl-*N*-methylpyrrole has two signals, one at δ = 6.33 ppm integrating to two protons and a single proton resonance at δ = 7.20 ppm.[135]

It was found that traditional nucleophilic acylation catalysts, such as DMAP (**39**), DABCO (**38**), and imidazole (**215**), showed little catalytic activity with conversion into *C*2-acyl pyrrole **219** no greater than the background rate, with pyridine only affording a small rate increase (Table 2, entries 2-5). When the weak Lewis base triethylamine was used as a catalyst the rate was not increased, however the more basic diisopropylethyl amine (DIPEA) did give a slight rate increase (Table 2, entries 7 and 8). However, the use of proton sponge, which is a much stronger Brønsted base, did not increase the reaction rate further (Table 2, entry 9). Pleasingly, the use of the bicyclic amidines DBU (**5**) and DBN (**6**) did give a significant rate increase (Table 2, entries 10 and 11), with 72% 2-benzoyl-*N*-methylpyrrole (**219**) formed after only 1.5 hours using 15 mol% DBN (**6**). The use of the DBN (**6**) and 1,2,4-triazole catalytic system, as described by

[†] An initial screen of solvents, solvent concentration, equivalents of acyl chloride and catalyst loading revealed these to be the best conditions.

Birman for the aminolysis and transesterification of esters,[136] did not further increase the rate (Table 2, entry 12). In all cases only the *C*2-acyl pyrrole **219** was observed, with no trace of the *C*3-regioisomer present in the crude ^{1}H NMR spectrum.

Table 2. Catalyst screen for the acylation of *N*-methylpyrrole (**167**).[a]



Entry	Catalyst	Time (h)	Conversion (%)[b,c]
1	-	1.5	30
2	DMAP (**39**)	1.5	31
3	DABCO (**38**)	1.5	34
4	Imidazole	1.5	33
5	Pyridine	1.5	45
6	Morpholine	1.5	29
7	Et_3N	1.5	36
8	$^iPr_2NEt$	1.5	52
9	Proton sponge	1.5	40
10	DBU (**5**)	1.5	60
11	DBN (**6**)	1.5	72
12	DBN (**6**) + 1,2,4-triazole	1.5	72
13	DBN (**6**)	4	95 (73)
14	-	8	87 (57)

[a]Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**213**). [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c]Isolated yields by column chromatography in parentheses.

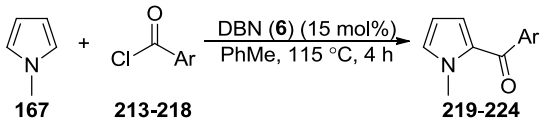
Further optimization using DBN (**6**) showed that increasing the reaction time to four hours gave essentially complete conversion into acyl pyrrole **219** as a single regioisomer (Table 2, entry 13). The crude reaction mixture was diluted with dichloromethane and washed with 1M HCl followed by 1M NaOH to remove the DBN (**6**) catalyst. The crude product was then purified by column chromatography to give a 73% isolated yield of 2-benzoyl-*N*-methylpyrrole (**219**). This compares with the uncatalysed acylation reaction that took eight hours to proceed to 87% conversion, affording acyl pyrrole **219** in only 57% isolated yield (Table 2, entry 14).

2.2.1 Scope of Acyl Chlorides

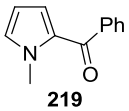
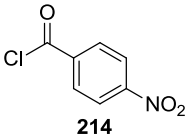
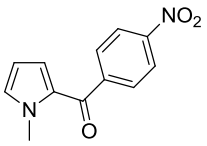
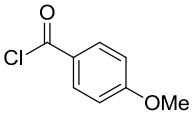
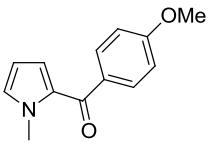
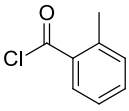
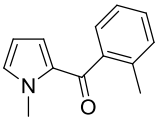
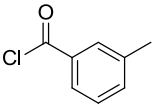
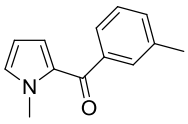
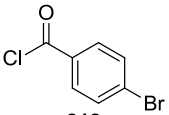
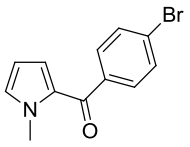
With optimised conditions in hand, the generality of this acylation protocol was tested using a range of aromatic acyl chlorides (**213**-**218**) for the acylation of *N*-methylpyrrole (**167**) using 15 mol% DBN (**6**) as a catalyst in toluene at reflux (Table 3). The quantitative conversions of these reactions were established by analysis of the crude ^{1}H NMR spectra using 2,5-dimethylfuran as an internal standard. The regioselectivities of the reactions was also confirmed by ^{1}H NMR spectroscopic analysis, as *C*2-acyl pyrroles generally exhibit three ^{1}H resonances between δ = 7 and 6 ppm, whereas the corresponding *C*3-acyl pyrroles usually have a characteristic pyrrole ring-proton signal above δ = 7 ppm.

It was found that the reaction with substituted benzoyl chlorides tolerated both strongly electron-withdrawing (*p*-NO_2) and electron-donating (*p*-OMe) substituents (**214** and **215**), with complete conversion into a single regioisomer and good isolated yields observed in both cases (Table 3, entries 2 and 3). The reduced isolated yields obtained when compared with the observed conversion values determined by ^{1}H NMR spectroscopic analysis are likely to be due to unwanted acid-catalysed polymerisation of the pyrrole products, which is a common problem in the isolation and purification of pyrrole compounds.[94] Next, the effect of the position of the aryl ring substituent was studied using *ortho*- and *meta*-toluoyl chloride (**216** and **217**) as acylating agents. It was found that the reactions using *o*- and *m*-toluoyl chloride (**216** and **217**) required longer reaction times than the *para*-substituted benzoyl chlorides. The reaction with *o*-toluoyl chloride (**216**) gave 100% conversion after eight hours, allowing 63% of the *C*2-acylated product (**222**) to be isolated by column chromatography (Table 3, entry 4). The reaction with *m*-toluoyl chloride (**217**) also required eight hours to proceed to completion, with 76% isolated yield obtained after chromatography (Table 3, entry 5). The longer reaction time for required for *o*-toluoyl chloride (**216**) is thought to be due to the increased steric demand at the reaction centre. The importance of the electronic nature of the *ortho*-substituent was also demonstrated by the fact that the reaction with *o*-nitrobenzoyl chloride did not work at all, with no conversion into acyl pyrrole observed by ^{1}H NMR spectroscopic analysis after twenty-four hours. The presence of a halogen substituent on the aryl ring was well tolerated, with the acylation reaction using *p*-bromobenzoyl chloride (**218**) giving complete conversion into a single regioisomer of product after four hours, allowing 70% of *C*2-acyl pyrrole **224** to be isolated (Table 3, entry 6).

Table 3. Acylation of *N*-methylpyrrole (**167**) with a range of aromatic acyl chlorides (**213-218**).[a]



167 213-218 219-224

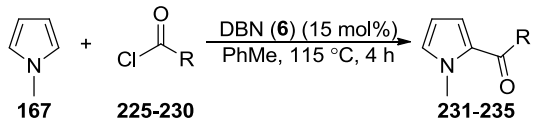
Entry	Acyl chloride (**213-218**)	Acyl pyrrole (**219-224**)	Conversion (%)[b,c]
1	 **213**	 **219**	95 (73)
2	 **214**	 **220**	100 (74)
3	 **215**	 **221**	100 (66)
4[d]	 **216**	 **222**	100 (63)
5[d]	 **217**	 **223**	100 (76)
6	 **218**	 **224**	100 (70)

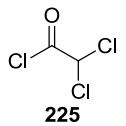
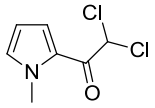
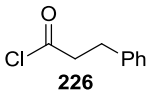
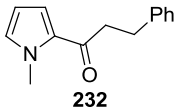
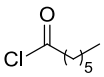
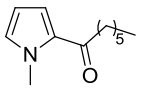
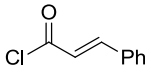
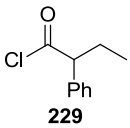
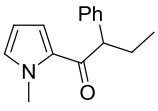
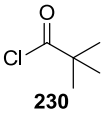
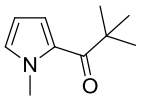
[a]Reactions performed on a 1 mmol scale using 1.2 mmol acyl chloride. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c]Isolated yields by column chromatography in parentheses. [d]8 hours reaction time.

Next, the acylation of *N*-methylpyrrole (**167**) with alkyl acyl chlorides (**225-230**) using 15 mol% DBN (**6**) as a catalyst in toluene at reflux was investigated (Table 4). It was found that the reactive dichloroacetyl chloride (**225**) gave complete conversion into the acylated product **231**, with only an acid/base work-up required to remove the DBN (**6**) catalyst to obtain an analytically pure sample of product (**231**) in 80% isolated yield (Table 4, entry 1). The straight

chain hydrocinnamoyl chloride (**226**), and heptanoyl chloride (**227**) were found to be just as active in the acylation reaction, with 100% conversion into product by ^{1}H NMR spectroscopic analysis and high isolated yields by column chromatography observed in both cases (Table 4, entries 2 and 3). However, the DBN (**6**) catalysed acylation reaction using unsaturated cinnamoyl chloride (**228**) was unsuccessful and, although all of the *N*-methylpyrrole (**167**) was consumed, there was no evidence of product by analysis of the crude ^{1}H NMR spectrum (Table 4, entry 4). The complete decomposition of the starting materials and/or products under the

Table 4. Acylation of *N*-methylpyrrole (**167**) with a range of alkyl acyl chlorides (**225**-**230**).[a]



Entry	Acyl chloride (**225**-**230**)	Acyl pyrrole (**231**-**235**)	Conversion (%)[b,c]
1	 **225**	 **231**	100 (80)
2	 **226**	 **232**	100 (70)
3	 **227**	 **233**	100 (82)
4	 **228**	-	100 (-)
5	 **229**	 **234**	58 (44)
6[d]	 **230**	 **235**	71 (63)

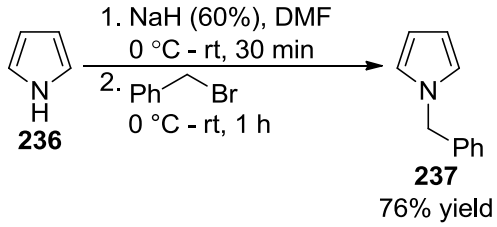
[a]Reactions performed on a 1 mmol scale using 1.2 mmol acyl chloride. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c]Isolated yields by column chromatography in parentheses. [d]8 hours reaction time.

reaction conditions is likely to be due to competing conjugate addition reactions that may also be promoted by the DBN (**6**) catalyst (see page 21). More sterically demanding acyl chlorides were found to react more slowly, with 2-phenylbutanoyl chloride (**229**) reacting to give only 58% conversion and 44% isolated yield of acylated product (**234**) in four hours (Table 4, entry 5). The bulkier pivaloyl chloride (**230**) also proved more sluggish, requiring a longer reaction time of eight hours to proceed to a reduced 71% conversion and 63% isolated yield (Table 4, entry 6). Increasing the reaction time beyond eight hours led to further consumption of *N*-methylpyrrole (**167**), however it also led to reduced isolated yields of the desired pivaloylated pyrrole product (**235**).

2.2.2 Scope of Substituted Pyrroles

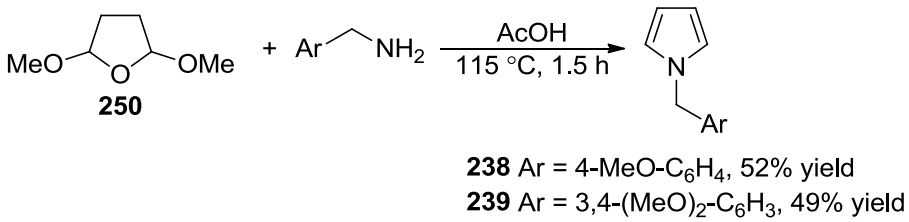
The organocatalytic Friedel-Crafts acylation methodology was then tested on a number of substituted pyrroles and *N*-protected pyrroles. The substituted pyrrole substrates were made *via* a number of different methods involving either the functionalization of pyrrole itself or construction of the pyrrole ring. The structures of the desired products were confirmed by comparison of their ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra with those in the literature.

N-Benzylpyrrole (**237**) was synthesised by alkylating pyrrole (**236**) with benzyl bromide (Scheme 44).[137] Firstly, pyrrole (**236**) was deprotonated using sodium hydride in DMF, before benzyl bromide was added dropwise and the reaction stirred for one hour. The crude reaction mixture was purified by column chromatography to afford *N*-benzylpyrrole (**237**) in 76% yield.



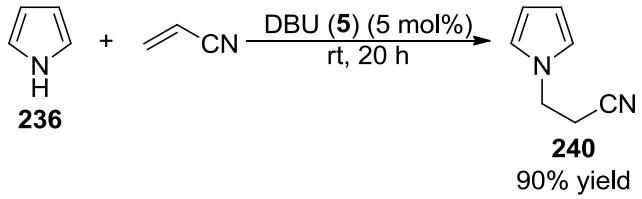
Scheme 44. Alkylation of pyrrole (**236**) with benzyl bromide to afford *N*-benzylpyrrole (**237**).

The Clausen-Kaas variation of the Paal-Knorr pyrrole synthesis was used to synthesise both *N*-*p*-methoxybenzyl- (PMB) and *N*-3,4-dimethoxybenzyl- (DBM) pyrrole (**238** and **239**) (Scheme 45).[138] Thus, a solution of 2,5-dimethoxytetrahydrofuran (**250**), the appropriately substituted benzylamine and glacial acetic acid were heated in a carousel tube at 115 °C for one and a half hours, before the reaction was quenched with sodium hydrogen carbonate and worked-up. The crude reaction mixtures were purified by column chromatography to give pure *N*-PMB- and *N*-DBM-pyrrole (**238** and **239**) in 52% and 49% yield respectively.



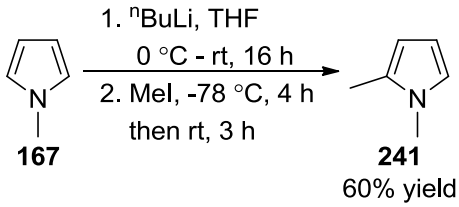
Scheme 45. The Clausen-Kaas variation of the Paal-Knorr pyrrole synthesis used to form *N*-PMB and *N*-DMB pyrrole (**238** and **239**).

The DBU (**5**) catalysed 1,4-conjugate addition of pyrrole (**236**) to acrylonitrile, as developed by Connon and co-workers (see page 21), was used to synthesise the cyanoethyl protected pyrrole **240** (Scheme 46).[68] A neat solution of pyrrole (**236**), acrylonitrile, and 1 mol% DBU (**5**) was stirred at room temperature overnight before the reaction was washed and extracted, providing the pure *N*-protected pyrrole **240** in 90% yield without the need for further purification.



Scheme 46. The DBU catalysed 1,4-conjugate addition of pyrrole (**236**) to acrylonitrile.

Finally, 1,2-dimethylpyrrole (**241**) was synthesised by alkylating *ortho*-lithiated *N*-methylpyrrole (**167**) with methyl iodide (Scheme 47).[139] Therefore, one equivalent of a 2.5 M solution of ^{n}BuLi in hexanes was added dropwise to solution a of *N*-methylpyrrole (**167**) in THF at -78 °C and the resulting reaction mixture was allowed to warm slowly to room temperature overnight. The reaction was again cooled to -78 °C before a solution of methyl iodide in THF was added. The solution was stirred for four hours at -78 °C before being allowed to warm to

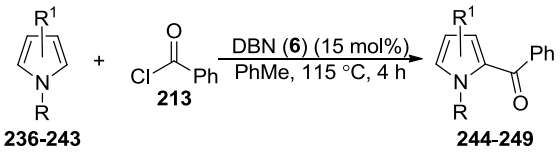


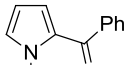
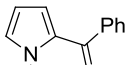
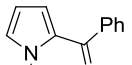
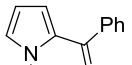
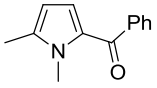
Scheme 47. Alkylation of *ortho*-lithiated *N*-methylpyrrole (**167**) with methyl iodide.

room temperature and stirred for another three hours. The crude reaction mixture was quenched with water, worked-up, and purified by Kugelrohr distillation to give 1,2-dimethylpyrrole (**241**) in a 60% yield.

These protected pyrroles were then subjected to our standard organocatalytic Friedel-Crafts acylation conditions using benzoyl chloride (**213**) as the acylating agent (Table 5). When unprotected pyrrole (**236**) was used, quantitative *N*-acylation was observed as determined by analysis of the integrals of the characteristic signals of the pyrrole ring protons in the crude ^{1}H NMR spectrum (Table 5, entry 1). However, the *C*2-acylation reactions were found to be successful for all of the *N*-alkyl pyrroles investigated, with *N*-benzyl-, *N*-PMB-, *N*-DMB-, and *N*-cyanoethyl- pyrroles (**237**-**240**) all successfully acylated with high conversions to give a single regioisomer of their respective products. The crude reaction mixtures were readily purified by column chromatography, providing the *C*2-acyl pyrroles (**245**-**248**) in reasonable isolated yields in all cases (Table 5, entries 2-5). It should be noted that all of these *N*-substituents have previously been used as protecting groups for pyrroles, with deprotection methods available for their removal to afford free *C*2-acyl NH-pyrroles in good yields.[94] The acylation reaction was shown to tolerate ring substitution, with 1,2-dimethylpyrrole (**241**) being acylated with 100% conversion observed in four hours, allowing 63% of the acyl pyrrole product (**249**) to be isolated (Table 5, entry 6). Electronically deactivated *N*-Boc and *N*-tosyl pyrroles (**242** and **243**) were not acylated under the standard conditions. Increasing the reaction time to twenty-four hours did not help, with no acylated products being observed in the crude ^{1}H NMR spectrum of either reaction (Table 5, entries 7 and 8). These results demonstrate the need for an electron rich pyrrole ring in the acylation reactions, as the less electron rich *N*-Boc and *N*-tosyl pyrroles (**242** and **243**) must not be nucleophilic enough to attack the DBN activated benzoyl chloride. This is also supported by the fact that no di-acylation was observed for any of the substrates.

Table 5. Acylation of substituted pyrroles (**236**-**243**) with benzoyl chloride (**213**).[a]



Entry	Pyrrole (**236**-**243**)	Acyl pyrrole (**244**-**249**)	Conversion (%)[b,c]
1	 **236**	 **244**	100 (-)
2	 **237**	 **245**	86 (56)
3	 **238**	 **246**	100 (79)
4	 **239**	 **247**	87 (62)
5	 **240**	 **248**	94 (73)
6	 **241**	 **249**	100 (63)
7	 **242**	-	0 (-)
8	 **243**	-	0 (-)

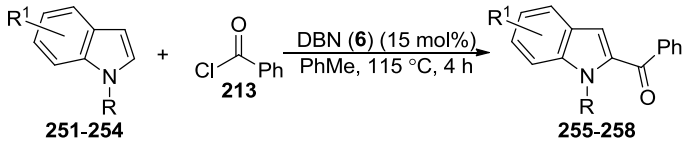
[a]Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**213**). [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c]Isolated yields by column chromatography in parentheses.

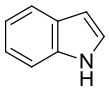
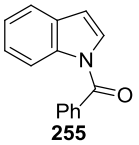
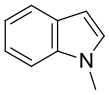
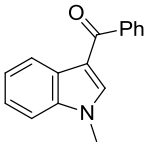
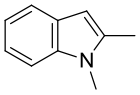
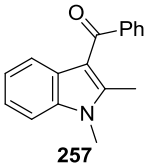
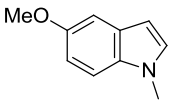
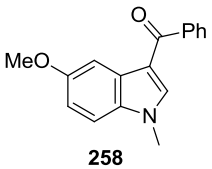
2.2.3 Acylation of Indoles

Given the success of the organocatalytic pyrrole *C*-acylation reactions, a logical extension was to apply the acylation protocol to substituted indoles (Table 6). As with pyrrole (**236**), when unsubstituted indole (**251**) was heated with benzoyl chloride (**213**) and 15 mol% DBN (**6**) in toluene at 115 °C, only the *N*-acylated product **255** was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture (Table 6, entry 1). Pleasingly, *N*-methylindole (**252**) was regioselectively acylated under these conditions in its *C*3 position as precedented, albeit in lower 65% conversion after four hours (Table 6, entry 2). Attempts to increase the conversion into acyl-indole **256** by increasing the reaction time beyond four hours were unsuccessful and led to a reduction in the amount of *C*3-acyl indole (**256**) recovered. The regioselectivity of the reaction was confirmed by ^{1}H TOCSY analysis of the isolated product, which isolates related spin systems signals within a molecule. This analysis showed that the remaining pyrrolic indole proton resonates at δ = 7.6 ppm and had a strong NOE interaction with the signal from the *N*-methyl protons, which is an interaction that would only be present in the *C*3-acyl indole (**256**).

The acylation reaction proceeded more smoothly with 1,2-dimethylindole (**253**) (prepared *via* *N*-alkylation of 2-methylindole), with complete conversion into *C*3-acyl indole **257** observed in four hours. The crude reaction mixture was purified by column chromatography to give an 88% yield of the acylated indole (**257**) (Table 6, entry 3). The acylation of indoles was shown to be sensitive to substitution in the benzenoid ring, as 5-methoxy-*N*-methylindole (**254**) only gave 57% conversion into *C*3-acyl product **258** in the DBN (**6**) catalysed reaction with benzoyl chloride (**213**) in four hours (Table 6, entry 4). As seen previously, attempts to increase conversion further by increasing the reaction time only led to a decrease in the amount of product isolated from the reaction.

Table 6. Acylation of substituted indoles (**251**-**254**) with benzoyl chloride (**213**).[a]



Entry	Indole (**251**-**254**)	Acyl indole (**255**-**258**)	Conversion (%)[b,c]
1	 **251**	 **255**	100 (-)
2[d]	 **252**	 **256**	65 (54)
3	 **253**	 **257**	100 (88)
4[d]	 **254**	 **258**	57 (40)

[a]Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**213**). [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c]Isolated yields by column chromatography in parentheses. [d]Attempts to increase the levels of conversion by increasing the reaction time to greater than four hours led to a drop in yield of the corresponding indole product.

2.2.4 Acylation of Other Heteroaromatic Compounds

As the DBN (**6**) catalysed Friedel-Crafts acylation was successful for both *N*-protected pyrroles and indoles, the scope of this catalytic protocol towards other heterocycles was investigated. Various heteroaromatic substrates including 2-methylfuran (**259**), 2-(trimethylsiloxy)furan (**260**), benzopyran (**261**), *N*-phenylpyrazole (**262**), and *N*-methylbenzopyrazole (**263**) were investigated in the reaction with benzoyl chloride using 15 mol% DBN (**6**) in toluene at 115 °C for twenty-four hours (Figure 5). However, crude ^{1}H NMR spectroscopic analysis showed that all of the reactions were unsuccessful, with starting material recovered quantitatively in all cases. Increasing catalyst loading had no effect, with one equivalent of DBN (**6**) failing to promote acylation of 2-methylfuran (**259**) under the standard reaction conditions. The use of microwave irradiation also had no effect on the reactivity of 2-methylfuran (**259**), with no

acylated products being observed in the crude ^{1}H NMR spectra after three hours of irradiation in toluene.

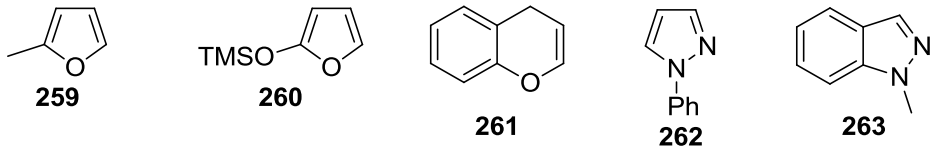
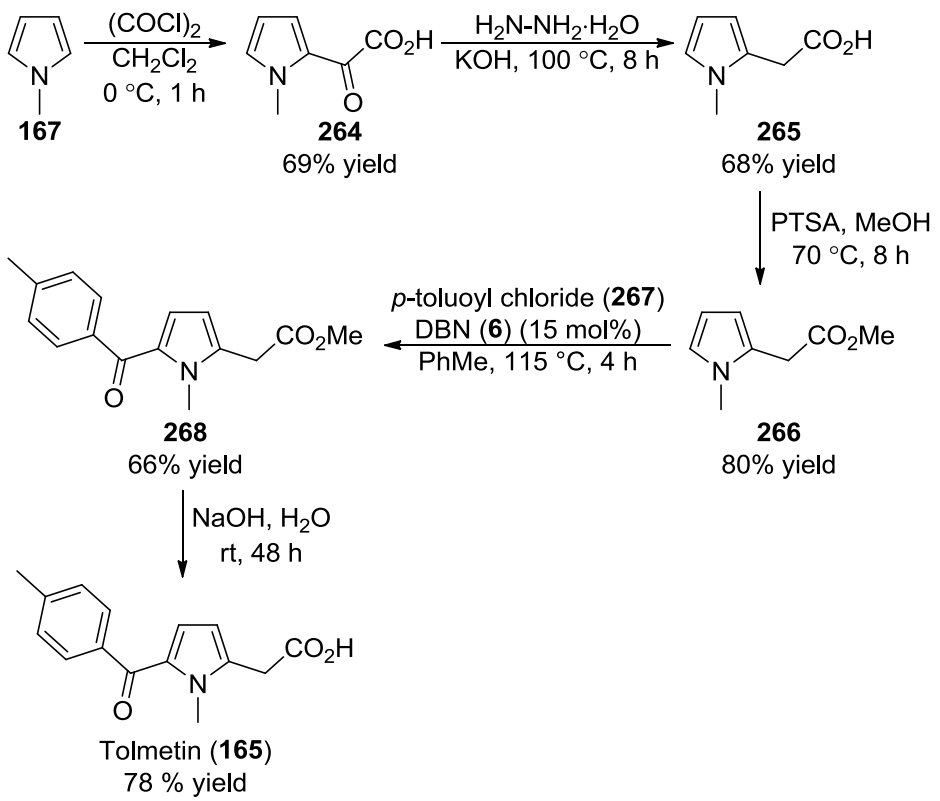


Figure 5. Heteroaromatic substrates for which the organocatalytic Friedel-Crafts acylation was unsuccessful.

2.2.5 Synthesis of Tolmetin

The synthetic utility of the DBN (**6**) catalysed acylation protocol was then demonstrated for the synthesis of the non-steroidal anti-inflammatory drug Tolmetin (**165**), whose pyrrole skeleton contains a *C*2 *p*-toluoyl substituent. The acylation step in previous syntheses of Tolmetin (**165**) has proved problematic, with low yields and poor regioselectivity reported in early syntheses.[140] Recently, Reddy has reported a new synthesis of Tolmetin (**165**), however, the key acylation step was performed under relatively harsh conditions by heating pyrrole ester **266** with *p*-toluoyl chloride (**267**) in *o*-xylene at 145 °C for twenty-four hours. Subsequent base catalysed hydrolysis of the ester functionality provided Tolmetin (**165**) in 55% yield over two steps.[140]

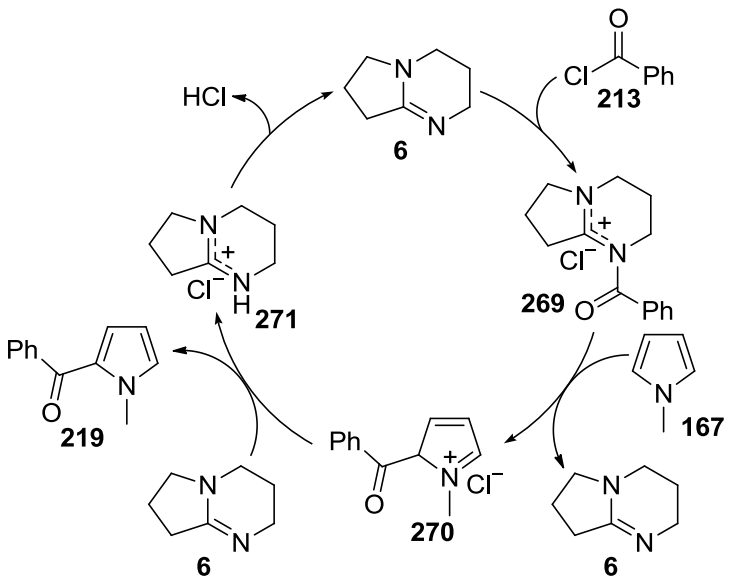
The key pyrrole ester intermediate **266** was synthesised in three steps from *N*-methylpyrrole (**167**) using Reddy's methodology (Scheme 48). Thus, *N*-methylpyrrole (**167**) was added dropwise to a solution of oxalyl chloride in dichloromethane at -10 °C, the resulting solution was stirred for one hour before potassium hydroxide was added to basify the reaction mixture. Upon work-up, the α-keto acid **264** was isolated in a 69% yield without the need for any further purification. Wolff-Kishner reduction of α-keto acid **264** using hydrazine hydrate in 20% w/w aqueous KOH provided acid **265**, which was isolated in 68% yield after purification *via* recrystallisation from diethyl ether and petrol. Esterification of acid **265** by heating with PTSA in methanol at reflux provided the pyrrole ester **266** in 80% yield after purification by column chromatography. Pyrrole ester **266** was then acylated using the organocatalysed Friedel-Crafts methodology by heating 1.2 equivalents of *p*-toluoyl chloride (**267**) and 15 mol% DBN (**6**) at reflux in toluene for four hours. Pleasingly, analysis of the crude ^{1}H NMR spectrum showed that the *C*2-acyl pyrrole **268** had been formed with 100% conversion and was isolated in 66% yield after column chromatography. Hydrolysis of methyl ester **268** using 2.5 M NaOH at room temperature provided Tolmetin (**165**), which was isolated in a 78% yield after trituration with diethyl ether.



Scheme 48. Synthesis of Tolmetin (**165**) using the DBN (**6**) catalysed Friedel-Crafts acylation as a key step.

2.2.6 Mechanistic Studies

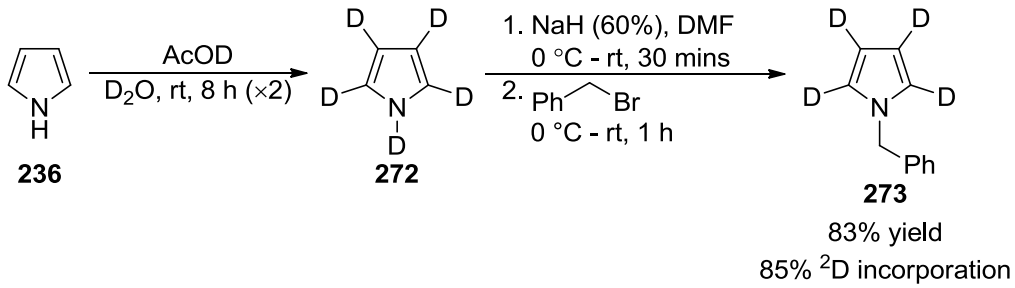
As the scope and synthetic utility of the DBN (**6**) catalysed Friedel-Crafts reaction had been demonstrated, the mechanism of the reaction was investigated to confirm that the DBN (**6**) was acting as a nucleophilic catalyst towards the acyl chloride. The proposed catalytic cycle of the reaction is shown in Scheme 49. Firstly, DBN (**6**) nucleophically attacks the acyl chloride (**213**), to generate an activated *N*-acyl DBN intermediate (**269**), which should be more susceptible to nucleophilic attack by the *N*-methylpyrrole (**167**) than the parent acyl chloride (**213**). Nucleophilic attack of *N*-methylpyrrole (**167**) on the *N*-acyl DBN intermediate (**269**) forms the *C*2-acylated intermediate **270** and regenerates the DBN (**6**) catalyst. As DBN (**6**) is a strong base, it seems reasonable that DBN (**6**) rearomatises intermediate **270** to release the *C*2-acylated product **219** and form DBN hydrochloride (**271**). The DBN hydrochloride (**271**) can then dissociate under the reaction conditions to release the catalyst to continue the catalytic cycle. The proposed catalytic cycle was investigated by considering the viability of each of these steps individually.



Scheme 49. Proposed mechanism for the DBN (**6**) catalysed *C*2-acylation of *N*-methylpyrrole (**167**).

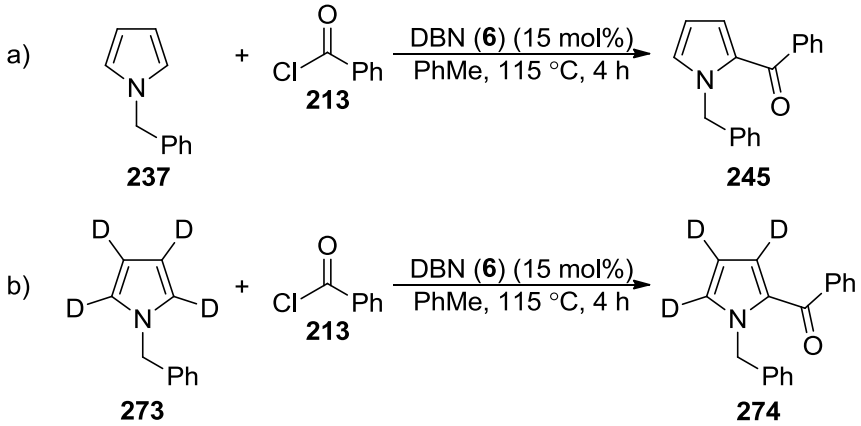
Firstly, we ruled out the possibility that DBN (**6**) was increasing the rate of reaction by simply acting as a base to rearomatise the acylated pyrrole intermediate (**270**). This was confirmed by performing a kinetic-isotope experiment to show that rearomatisation was not the rate-determining step. Therefore, the rates of the acylation reactions for both *N*-benzylpyrrole (**237**) and *N*-benzyl-*D*4-pyrrole (**273**) with benzoyl chloride (**213**) were studied. If the deprotonation step is rate-determining, a positive primary kinetic isotope effect would be expected, however if the rearomatisation step is not rate-determining then no isotope effect would be expected and the rates of the two reactions should be the same.

The kinetic isotope experiments were performed using *N*-benzyl-D_4-pyrrole (**273**) instead of *N*-methyl-*D*4-pyrrole as the latter is volatile and difficult to prepare. Initially, D_5-pyrrole (**272**) was synthesised by allowing pyrrole (**236**), acetic acid-D_1, and D_2O to equilibrate at room temperature for eight hours. After neutralisation of the reaction mixture with potassium carbonate and work-up the reaction was repeated to ensure maximum deuterium incorporation (Scheme 50).[141] The D_5-pyrrole (**272**) was then alkylated using sodium hydride and benzyl bromide, to provide *N*-benzyl-D_4-pyrrole (**273**) in 83% yield after purification by column chromatography.[137] Comparison of the relative integrals of the benzyl protons at δ = 5.09 ppm in the ^{1}H NMR spectrum of the product with the integrals of the remaining pyrrole protons at δ = 6.72 and 6.22 ppm revealed that 85% deuterium incorporation had been achieved.



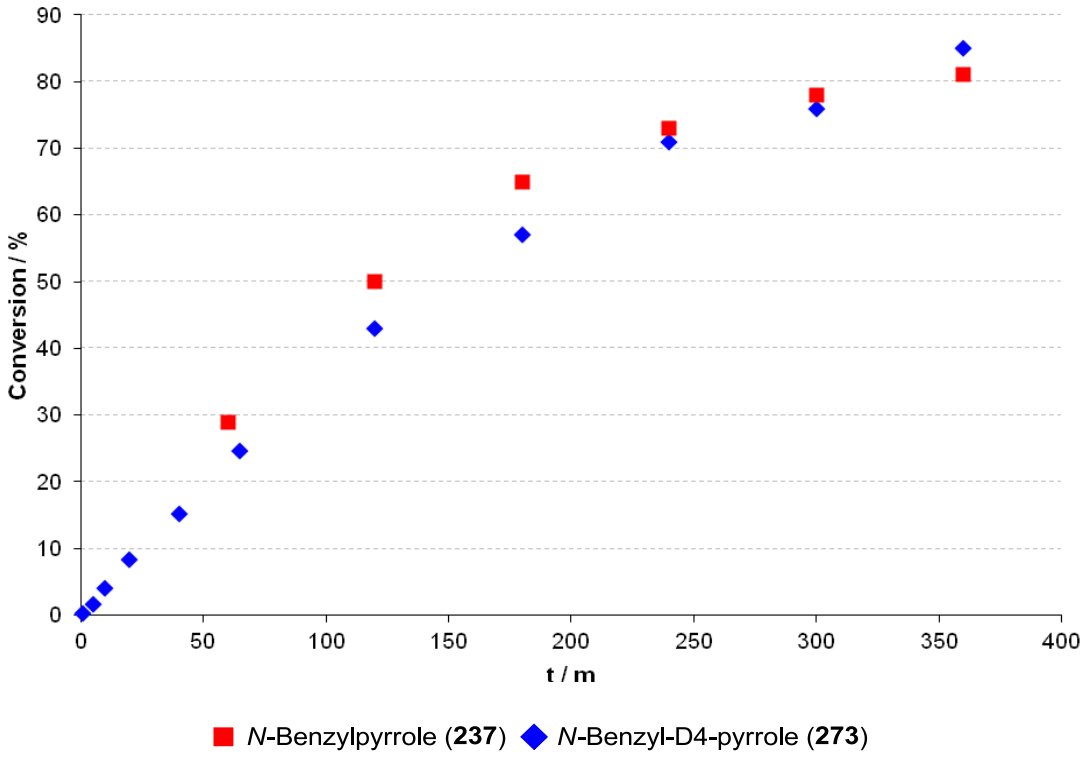
Scheme 50. Preparation of *N*-benzyl-D_4-pyrrole (**273**).

The rates of the DBN (**6**) catalysed acylation reactions of both *N*-benzylpyrrole (**237**) and *N*-benzyl-*D*4-pyrrole (**273**) with benzoyl chloride (**213**) were measured by taking aliquots of the two reaction mixtures and analysing them by ^{1}H NMR spectroscopy (Scheme 51). Comparison of the integrals of the benzyl proton signals in the ^{1}H NMR spectrum from the remaining starting material, at δ = 5.09 ppm, with the product, at δ = 5.57 ppm, allowed the conversions of the reactions at each time interval to be accurately measured, the results of which are shown in Graph 1.



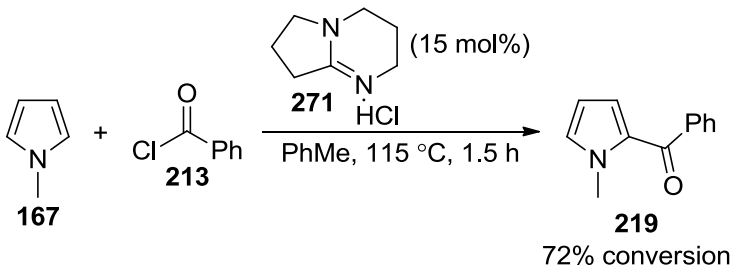
Scheme 51. Experiments performed using a) *N*-benzylpyrrole (**237**) and b) *N*-benzyl-D_4-pyrrole (**273**) to determine if rearomatisation is the rate-determining step in the reaction mechanism.

The results from the two kinetic experiments showed that there was essentially no difference in the rate of acylation of *N*-benzylpyrrole (**237**) and *N*-benzyl-*D*4-pyrrole (**273**) with benzoyl chloride (**213**) (Graph 1). As there was no observable kinetic isotope effect, the rearomatisation of the *C*2-acyl pyrrole intermediate (**270**) cannot be the rate-determining step and therefore the DBN (**6**) cannot be acting solely as a base to increase the rate of the reaction. More aliquots at shorter time intervals were taken for the acylation reaction using *N*-benzylpyrrole (**237**), with the smooth curve obtained suggesting that a single mechanism operates throughout the reaction.



Graph 1. Data from the kinetic isotope experiments comparing the rate of the DBN (**6**) catalysed acylations of *N*-benzylpyrrole (**237**) and *N*-benzyl-D_4-pyrrole (**273**) with benzoyl chloride (**213**).

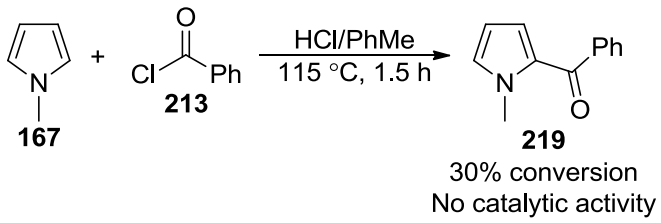
The rearomatisation step, whilst not rate-determining, generates DBN hydrochloride (**271**) that must then dissociate to release the DBN (**6**) to continue in the catalytic cycle. It is proposed that at the temperature of the reaction (115 °C) this dissociation process is facile, with the equilibrium of dissociation being driven towards formation of the amidine catalyst by the low solubility of HCl in toluene. This hypothesis is supported by a number of experimental observations. It was found that the standard acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) using 15 mol% DBN (**6**) releases HCl gas from the solution over the course of the reaction. A sample of DBN hydrochloride (**271**), made from DBN (**6**) and ethereal HCl,



Scheme 52. DBN hydrochloride (**271**) serves as a catalytic precursor, demonstrating that it readily dissociates under the reaction conditions.

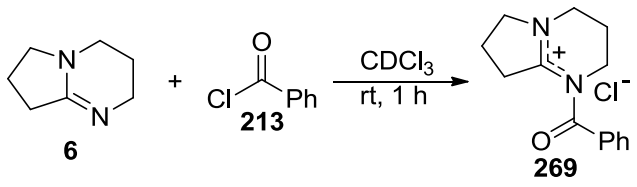
was also shown to release HCl gas when heated in toluene at reflux. DBN hydrochloride (**271**) was also found to serve as a catalytic precursor in the standard acylation reaction, with 15 mol% DBN hydrochloride (**271**) giving the same 72% conversion into *C*2-acyl product **219** as 15 mol% DBN (**6**) in 1.5 hours (Scheme 52 and Table 2, entry 11).

Next, it was confirmed that the reaction was not Brønsted acid catalysed by adventitious HCl generated in the reaction. The acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) was performed in a saturated solution of HCl in toluene at 115 °C for 1.5 hours (Scheme 53). ^{1}H NMR spectroscopic analysis of the reaction mixture, using 2,5-dimethylfuran as an internal standard, showed that the reaction had gone to 30% completion, which is the same as for the uncatalysed reaction without added HCl (Table 2, entry 1).



Scheme 53. The acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) is not Brønsted acid catalysed by HCl.

With other potential roles of the DBN (**6**) and the presence of DBN hydrochloride (**271**) ruled out as the source of catalysis, the proposed nucleophilic activation step of the acyl chloride by DBN (**6**) was investigated. In order to prove this hypothesis, it was decided to attempt to characterise and isolate the proposed *N*-benzoyl DBN intermediate (**269**). Therefore, a 1:1 mixture of DBN (**6**) and benzoyl chloride (**213**) was stirred in chloroform-D and the resulting solution analysed (Scheme 54). High-resolution mass-spectrometry confirmed the presence of a



Scheme 54. A 1:1 mixture of DBN (**6**) and benzoyl chloride (**213**) forms a quantitative amount of *N*-benzoyl DBN salt (**269**).

positively charged ion with the correct molecular weight for the *N*-benzoyl DBN intermediate (**269**). The solution was found to contain a single carbonyl resonance in its infrared spectrum at

1709 cm^{-1} that is different from the carbonyl stretch of benzoyl chloride (**213**), which resonates at 1770 cm^{-1}.

^{1}H NMR spectroscopic analysis of the solution showed that a single species had been formed whose spectrum was consistent with the formation of *N*-benzoyl DBN **269**, whilst no resonances corresponding to free DBN (**6**) were present in the spectrum (Figure 6). The aromatic protons of the compounds benzoyl fragment were shifted approximately 0.2 ppm upfield compared with the signals in free benzoyl chloride (**213**), whilst the signals for the protons of the amidine fragment were shifted downfield. The most dramatic deshielding (approximately 0.7 ppm downfield) was observed for the three pairs of protons adjacent to the two nitrogen atoms, suggesting that the positive charge of the intermediate is distributed

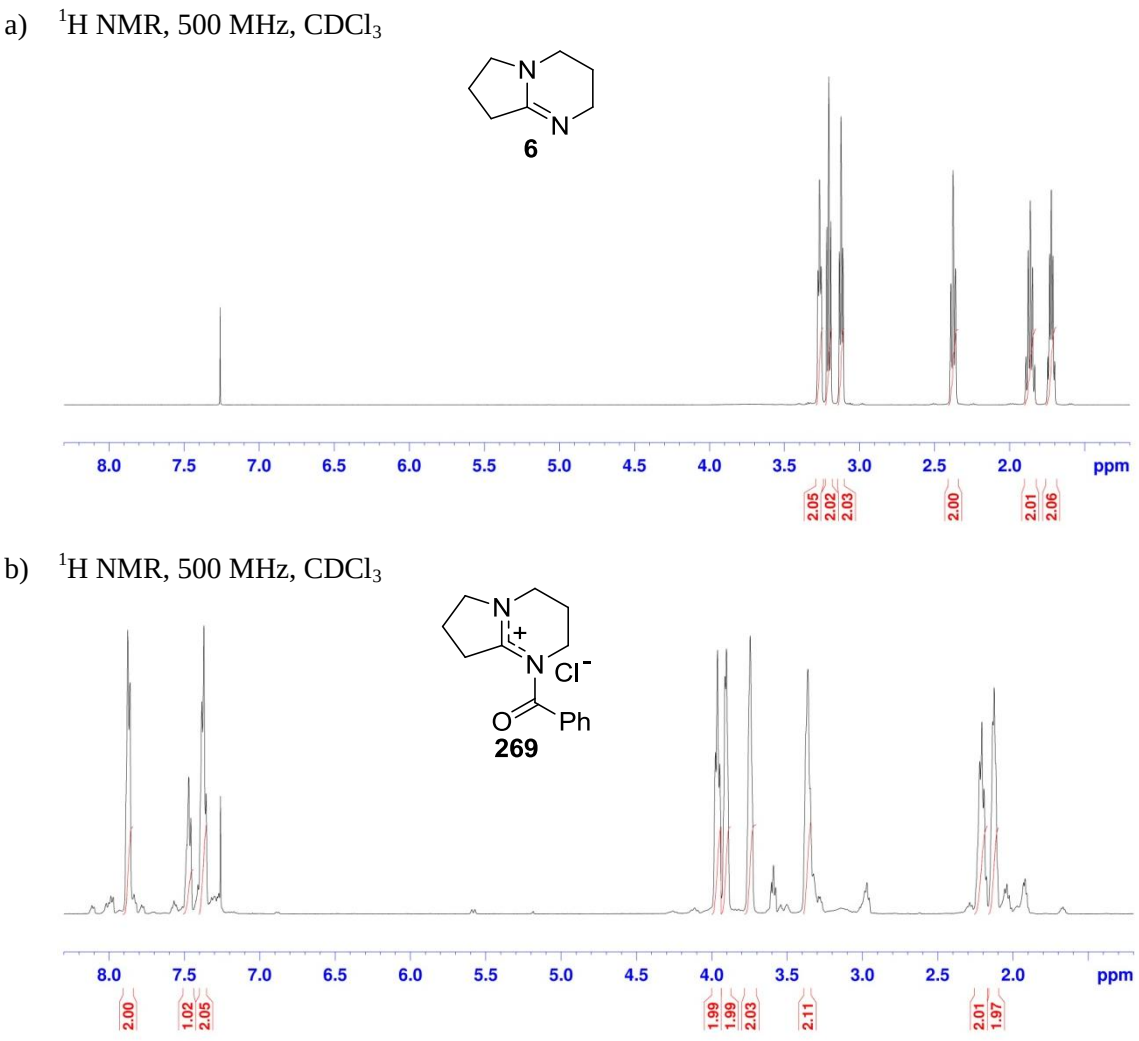
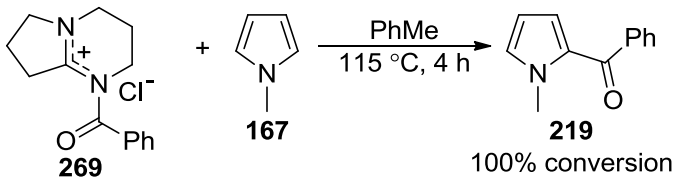


Figure 6. 500 MHz ^{1}H NMR spectra of a) DBN (**6**) and b) the intermediate formed from a 1:1 mixture of DBN (**6**) and benzoyl chloride (**213**).

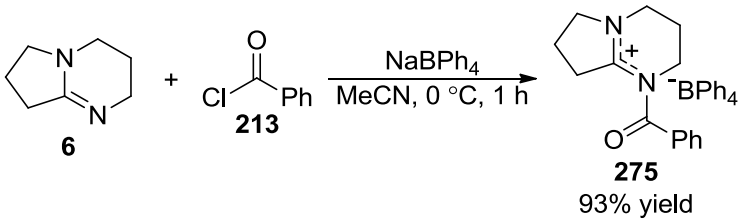
between both nitrogen atoms. ^{1}H NOESY analysis of the solution revealed that the *N*-acyl group was attached to the non-bridgehead nitrogen atom and has a conformational preference for its phenyl group being directed away from its five-membered ring.

Importantly, close analysis of the 500 MHz ^{1}H NMR spectrum of a sample of the standard acylation reaction using 15 mol% DBN (**6**) revealed the presence of a quantitative amount of this *N*-benzoyl DBN species **269**, with no resonances corresponding to any free DBN (**6**). As DBN (**6**) and benzoyl chloride (**213**) react almost immediately at room temperature to form the *N*-benzoyl DBN species (**269**), it is proposed that nucleophilic attack of the *N*-methylpyrrole (**167**) on intermediate **269** is the rate-determining step in the acylation reaction. This is again supported by the presence of *N*-benzoyl-DBN (**269**) in the ^{1}H NMR spectra throughout the course of the acylation reaction when using 15 mol% DBN (**6**) as a catalyst. In order to confirm that *N*-benzoyl DBN (**269**) was a catalytically active intermediate, a stoichiometric amount was reacted with *N*-methylpyrrole (**167**), which gave the corresponding *C*2-acyl pyrrole **219** in quantitative yield (Scheme 55).



Scheme 55. *N*-Benzoyl DBN intermediate (**269**) reacts quantitatively with *N*-methylpyrrole (**167**) to form *C*2-acyl pyrrole (**219**).

Attempts to obtain X-ray quality crystals of the *N*-benzoyl DBN salt (**269**) with chloride as counter-ion were unsuccessful as the salt that precipitated out of solution was unstable and hygroscopic. Therefore, attempts were made to exchange the chloride counter-ion for a more stable counter-ion. King and Bryant successfully used chloride counter-ion exchange to obtain X-ray crystal structures of *N*-acyl-DMAP salts,[142-143] whilst Birman and co-workers have also used counter-ion exchange to obtain X-ray crystal structures of *N*-acyl-2,3-dihydroimidazo[1,2-*a*]pyridines that are intermediates in acyl transfer reactions for kinetic resolution reactions of alcohols.[144] Using this method, the chloride counter-ion of the *N*-benzoyl DBN salt (**269**) was exchanged for both tetrafluoroborate and hexafluorophosphate, but in both cases the resulting salts were unstable and hygroscopic. However, exchanging the chloride counter-ion for tetraphenylborate by stirring a solution of DBN (**6**), benzoyl chloride (**213**), and sodium tetraphenylborate in acetonitrile did form an air stable solid (Scheme 56). The *N*-benzoyl DBN



Scheme 56. Exchanging the chloride counter-ion with tetraphenylborate allowed an air stable crystalline *N*-benzoyl DBN salt (**275**) to be isolated.

tetraphenylborate salt (**275**) was successfully re-crystallised from dichloromethane and hexane, allowing suitable crystals to be obtained for X-ray crystallographic analysis (Figure 7and Figure 8).

The X-ray crystal structure of the *N*-benzoyl DBN salt (**275**) confirms that the benzoyl fragment is attached to N1. The N1-C8 bond length of 1.349 Å and the N2-C8 bond length of 1.310 Å are intermediate between that of a N-C single bond and a N-C double bond, supporting the ^{1}H NMR spectroscopic evidence that the positive charge is delocalised over both nitrogen atoms. Interestingly, the carbonyl group of the *N*-benzoyl DBN salt (**275**) lies out of the plane of the delocalised amidine system, with an angle of 36.1° between the N1-C8-N2 and N1-C1-O1 planes (Figure 8). The fact that the carbonyl group lies out of the plane may explain why DBN (**6**) exhibits catalytic activity, whilst traditional acyl transfer catalysts such as DMAP (**39**) or

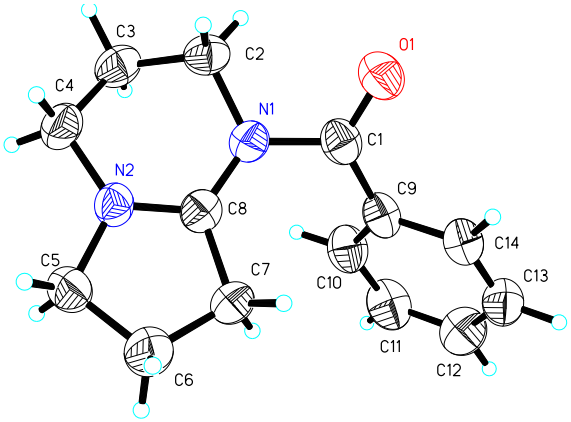


Figure 7. X-ray crystal structure of *N*-benzoyl DBN·BPh_4 salt (**275**). Thermal ellipsoids shown at the 50% probability level. Tetraphenylborate counter-ion not shown for clarity.

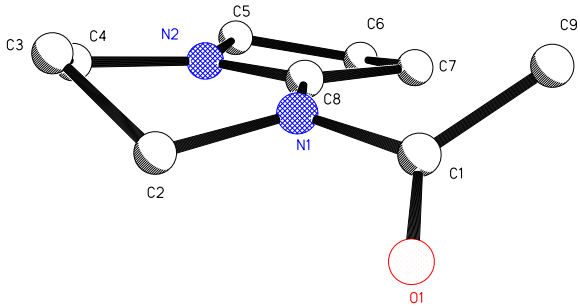


Figure 8. X-ray crystal structure of the *N*-benzoyl DBN·BPh_4 salt (**275**) reveals a 36.1° angle between the carbonyl and the amidine ring. Tetraphenylborate counter-ion not shown for clarity.

pyridine showed little activity in these acylation reactions (Table 2). Crystal structures of *N*-acyl DMAP systems reveal that the acyl group and the pyridine fragment lie in the same plane.[142-144] This is advantageous in acylation reactions where an anhydride is used as the acyl source, as the planar *N*-acyl DMAP intermediate is stabilised and thus the equilibrium between the anhydride and DMAP (**39**) derivative is more favourable.[145-147] Indeed, variable-temperature NMR spectroscopy experiments have shown that a mixture of PPY and acetic anhydride in $CDCl_3$ contains 5-10% *N*-acetylpyridinium acetate.[148] Whilst this equilibrium position is important for acylations using acid anhydrides, DMAP derivatives react quantitatively with acyl chlorides to give planar *N*-acyl pyridinium species. Therefore, it is the reactivity of the intermediate *N*-acyl intermediate, and not how much is formed, which determines the rate of the reaction. In our case, DBN (**6**) reacts quantitatively with the acyl chloride to give an *N*-acyl DBN intermediate (**269**) whose "out of plane" carbonyl group is less conjugated with the amidine ring, which may explain its increased reactivity towards nucleophilic attack.

2.3 Conclusions

In conclusion, the first organocatalytic Friedel-Crafts acylation reaction for the regioselective synthesis of *C*2-acyl pyrroles and *C*3-acyl indoles has been developed. The optimised protocol uses 15 mol% DBN (**6**) as a catalyst and can be used for the acylation of a number of pyrroles and indoles with a range of acyl chlorides. The synthetic utility of the process towards the synthesis of biologically active compounds has been demonstrated for the synthesis of the non-steroidal anti-inflammatory drug Tolmetin (**165**). Detailed mechanistic studies and characterisation of the key *N*-benzoyl DBN intermediate (**269**) suggest that DBN (**6**) functions as a nucleophilic catalyst to activate the acyl chloride in these reactions.

3 *N*-Acyl DBN·BPh_4 Salt Acylations

3.1 Introduction

As discussed in the previous chapter, investigation of the mechanism of the DBN (**6**) catalysed Friedel-Crafts acylation reaction (Chapter 2, page 52) resulted in isolation of a crystalline *N*-benzoyl DBN tetraphenylborate (**275**) salt, providing structural information about the proposed intermediate in the reaction. Consequently, due to the air stable and crystalline nature of this salt, it was decided to investigate the use of *N*-acyl DBN salts as stoichiometric acylating agents for a range of nucleophiles.

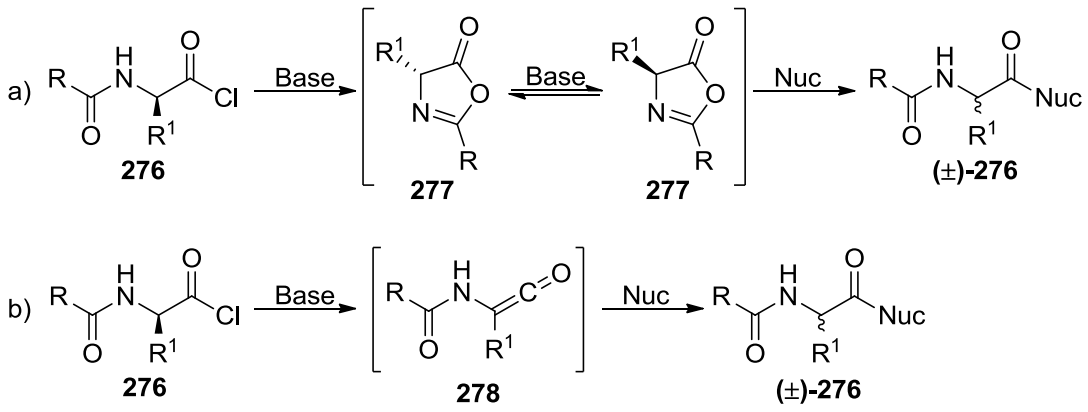
3.1.1 Acylation Strategies

The acylation reaction is one of the most significant and widely used reactions in organic chemistry. Acylations are essential for life, with proteins synthesised through a series of *N*-acylations on the ribosome, whilst fatty acid synthesis utilises a series of acyl transfer reactions for chain extension that are mediated by multi-component acyl-carrier proteins.[149] Acylation reactions are also one of the most widely used reactions in the pharmaceutical industry, with *N*-acylation reactions of amines to form amides being widely used for the synthesis of drug molecules on an industrial scale.[150]

Nature uses a number of different acyl transfer units; for example, in protein synthesis the acyl unit is carried by tRNA whereas acetyl-CoA is the acyl source in fatty acid synthesis.[149] Synthetic organic chemistry protocols employ a large number of different acyl sources, as well as an extensive range of catalysts to increase the rates of acylation reactions. Of all the potential acyl sources, acyl chlorides and acid anhydrides are the most widely used. The Schotten-Baumann reaction, first described in 1884, between amines or alcohols and acyl chlorides or acid anhydrides in the presence of aqueous base is the foundation of synthetic acylation reactions.[151] Modern variations of the original reaction are usually performed in organic solvents and utilise acyl transfer catalysts such as DMAP (**39**) and its derivatives, or Lewis acid catalysts,[148,152-153] although uncatalysed versions in organic solvents have also been reported.[154-155]

The use of carboxylic acids as acyl sources, in particular the coupling of amino acids for peptide synthesis, has generated much interest and investigation. The direct reaction between an acid and an amine usually results in salt formation rather than acylation. Although acid-amine salts can be condensed at high temperatures (140 – 180 °C),[156] the conditions are impractical and

often incompatible with other functionality. A common solution to this problem is to first convert the acid to an acyl chloride however, whilst this is straightforward for simple substrates, there are many problems encountered with acyl chlorides of more complex substrates. For example, the potential of acyl chlorides to undergo hydrolysis and/or racemisation limits their use in peptide coupling. Acyl chlorides of peptides (**276**) readily racemise under basic coupling conditions through the formation of an azlactone intermediate (**277**) (Scheme 57a), or *via* ketene (**278**) formation (Scheme 57b).[157]



Scheme 57. Potential of acyl chlorides of peptides (**276**) to undergo racemisation through a) azlactone (**277**) formation or b) ketene (**278**) formation.[157]

Consequently, numerous coupling reagents have been developed that activate acids towards nucleophilic addition of amines and alcohols in a one-pot procedure. Coupling reagents based on carbodiimide (**279**), *N*-acylimidazoles (**280**), phosphonium salts (**281**), and guanidinium salts (**282**) (Figure 9) are regularly used in peptide synthesis. There are many variations of these basic structures, as well as other types of coupling agents, all of which have been extensively reviewed in the literature.[157-162]

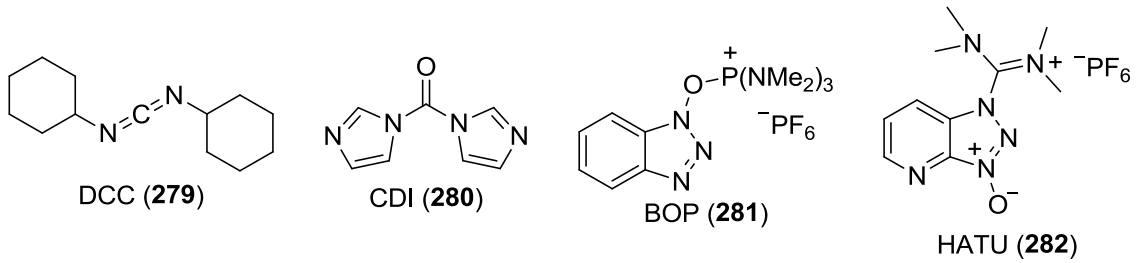


Figure 9. Examples of common peptide coupling agents.

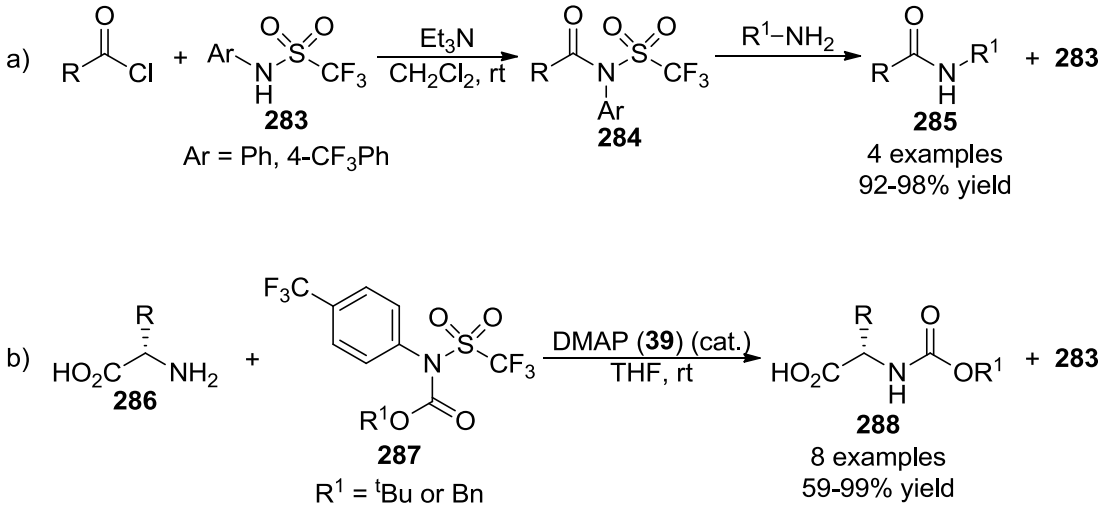
However, the use of such coupling reagents is often expensive and wasteful, as a stoichiometric amount of by-product is always produced alongside the desired amide. This drawback has led

increasingly to the development of more atom-economical non-metal and metal catalysed acylation protocols.[163]

3.1.2 Stoichiometric Acyl Transfer Agents

Alongside the fact that amino acid acyl chlorides are largely unavailable, there are other problems associated with the use of acyl chlorides and acid anhydrides in acylation reactions. For example, the reactions of amines with acyl chlorides are often highly exothermic, whilst anhydrides can form imides as side-products when reacted with primary amines.[164] Many acyl chlorides are also air sensitive and are hydrolysed by moisture to form acids, releasing HCl gas in the process. This can not only make some acyl chlorides practically difficult to use, but can also cause problems when acid sensitive functionality is present within the reacting molecules. Therefore, a number of alternatives have been sought to avoid the problems associated with using acyl chlorides for acylation reactions.

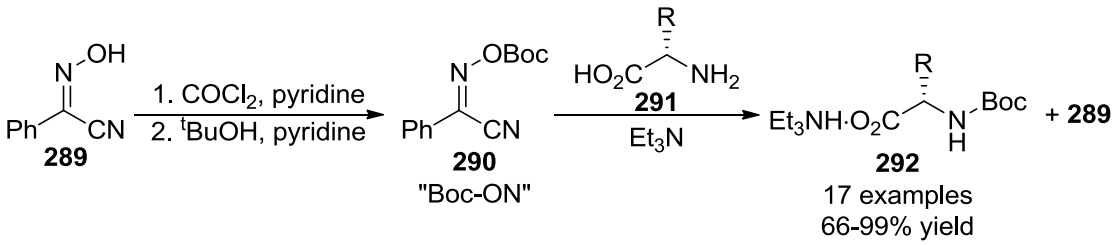
An early example of air stable and crystalline alternatives to acyl chlorides were *N*-acyl-*N*-phenyl triflamides (**284**). Hendrickson and Bergeron synthesised a small range of *N*-acyl-*N*-phenyl triflamides by either reacting *N*-phenyl triflamide (**283**) with an acyl chloride or, alternatively, reacting a deprotonated amide with triflic anhydride. The *N*-acyl triflamides (**284**) were subsequently shown to be efficient acylating agents for a small number of primary amines (Scheme 58a).[165] Almost 26 years after this initial report, Tomioka and co-workers reported that *N*-Boc and *N*-Cbz derivatives of *N*-4-(trifluoromethyl)benzene triflamide (**287**) could be used



Scheme 58. *N*-Aryl triflamides for a) the acylation of amines and b) Boc and Cbz protection of amino acids.[165-166]

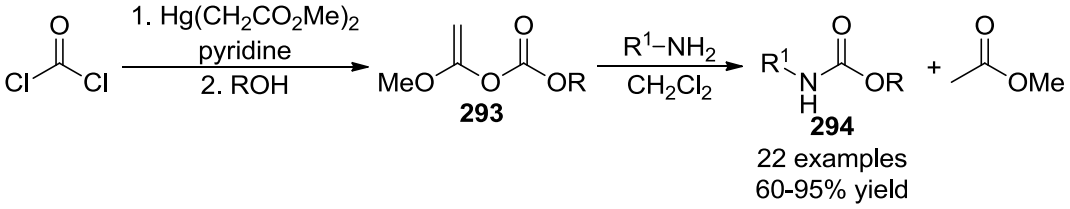
for the chemoselective protection of primary amines in the presence of secondary amines. They also showed that these reagents could efficiently protect amino acids, although in some cases catalytic amounts of DMAP (**39**) were required (Scheme 58b).[166]

Itoh *et al*. were the first to report the use of the oxime carbonate **290** (now commercially available as Boc-ON) for the Boc protection of amino acids (Scheme 59). Initially a range of oxime carbonates was synthesised by reacting oximes with phosgene followed by *t*-butanol. It was found that Boc-ON (**290**) was the most favourable oxime carbonate made in terms of stability and it was shown that it reacted with amino acids under mild conditions, with the oxime by-product conveniently removed through extraction of the reaction mixture with ethyl acetate.[167]



Scheme 59. Oxime carbonate (**290**, Boc-ON) as a Boc protecting agent.[167]

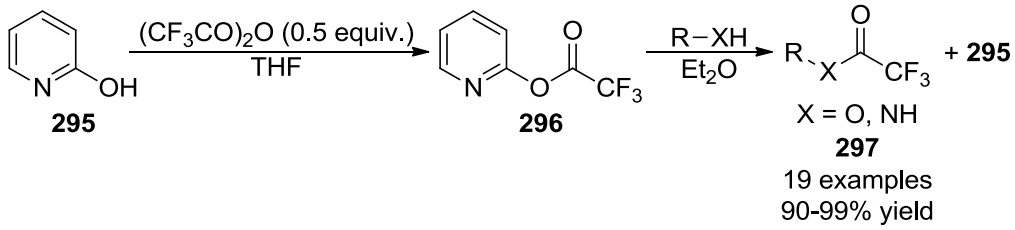
In 1982, Tamura *et al*. synthesised a range of alkyl α-methoxyvinyl carbonates (**293**) as alternatives to chloroformates for the carbamate protection of amines and amino acids. The vinyl carbonates (**293**) react with a wide range of amines and amino acids at room temperature without the need for added base, whilst the by-product is volatile methyl acetate. However, the synthesis of the vinyl carbonates (**293**) involves addition of a mercurial enolate equivalent to phosgene before the addition of an alcohol (Scheme 60).[168]



Scheme 60. Alkyl α-methoxyvinyl carbonates (**293**) for the carbamate protection of amines.[168]

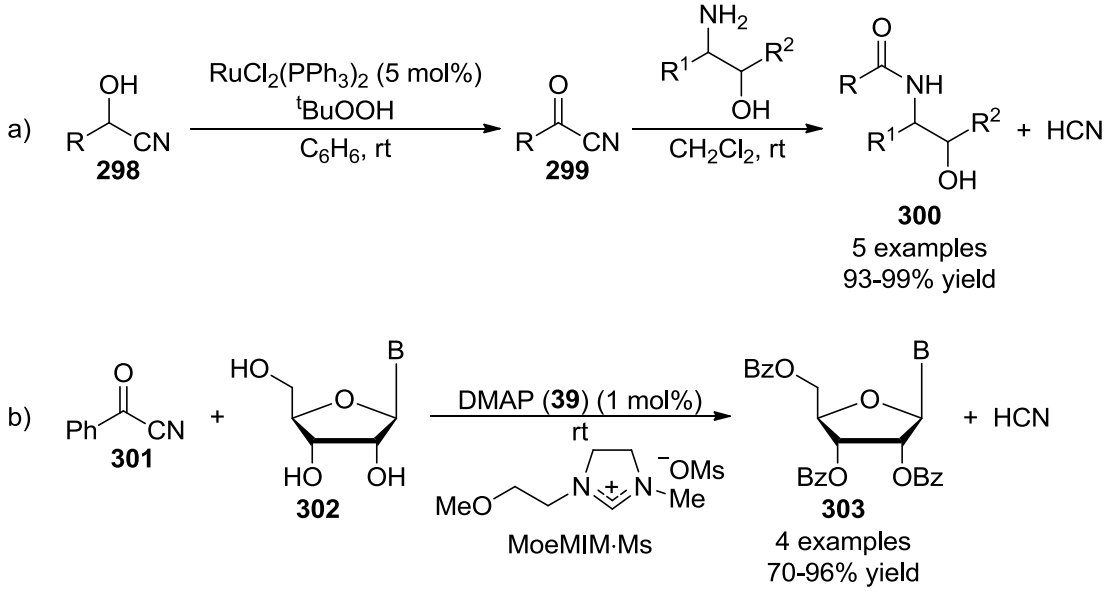
Keumi and co-workers have prepared 2-(trifluoroacetyloxy)pyridine (**296**) as an alternative to volatile and air sensitive trifluoroacetic anhydride for the trifluoroacetylation of alcohols and amines (Scheme 61). The reaction works for a range of substrates, with the 2-pyridinol by-

product precipitating from the reaction mixture upon cooling, allowing ester and amide products to be isolated in high yields.[169] O'Sullivan *et al*. and Prasad *et al*. independently reported the advantages of ethyl trifluoroacetate over trifluoroacetic acid for chemoselective trifluoroacetylation. Whilst trifluoroacetic acid reacts with both primary and secondary amines, less reactive ethyl trifluoroacetate can be used to selectively acylate the primary amine functionalities of polyamines.[170-171]



Scheme 61. Use of 2-(trifluoroacetyloxy)pyridine (**296**) for the trifluoroacetylation of alcohols and amines.[169]

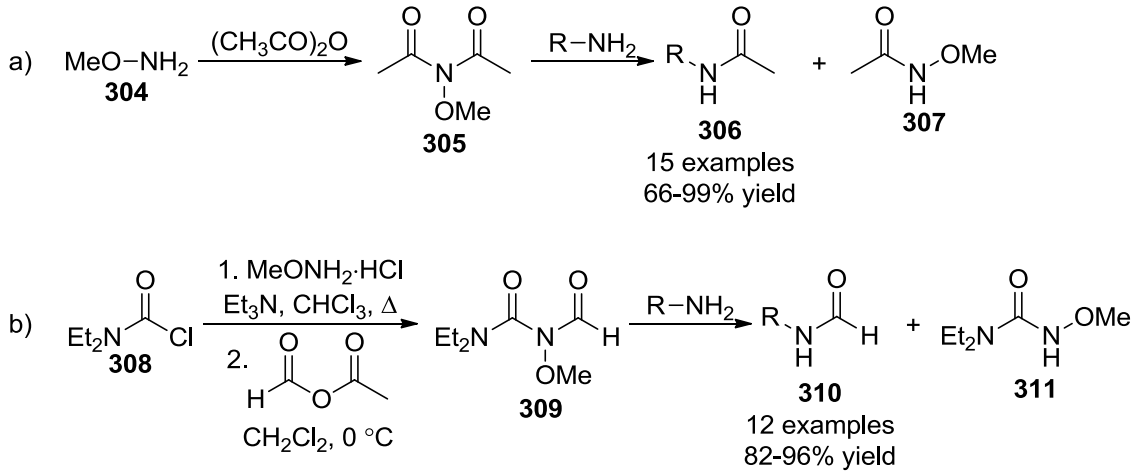
In 1954, acyl cyanides (**299**) were first reported as an alternative to acyl chlorides in acylation reactions.[172] Murahashi and Naota reported an efficient synthesis of acyl cyanides (**299**) through the ruthenium catalysed oxidation of the corresponding cyanohydrins (**298**) with *t*-butylhydroperoxide.[173-174] These acyl cyanides (**299**) were shown to be highly chemoselective acylating agents, with only *N*-acylation observed in their reaction with a number of amino alcohols (Scheme 62a). The use of cyanohydrins (**298**) also allowed acyl cyanides (**299**) of



Scheme 62. Acyl cyanides (**299**) as chemoselective acylating agents for a) *N*-acylation of amino alcohols and b) *O*-acylation of nucleobases (**302**) in an ionic liquid.[173-174,176-177]

unstable acyl chlorides to be prepared from their corresponding aldehydes.[175] More recently, Prasad *et al*. showed that benzoyl cyanide (**301**) can be used in an ionic liquid to selectively *O*-benzoylate nucleosides (**303**), with the free amines of the nucleobases remaining unreacted (Scheme 62b). The reversal in chemoselectivity observed in ionic liquid compared with organic solvent is attributed to the fact that OH bonds are highly polarized in ionic liquids and thus become more reactive than amino groups.[176-177] However, the use of acyl cyanides as alternatives to acyl chlorides and acid anhydrides is limited due to the release of highly toxic HCN during the acylation step.

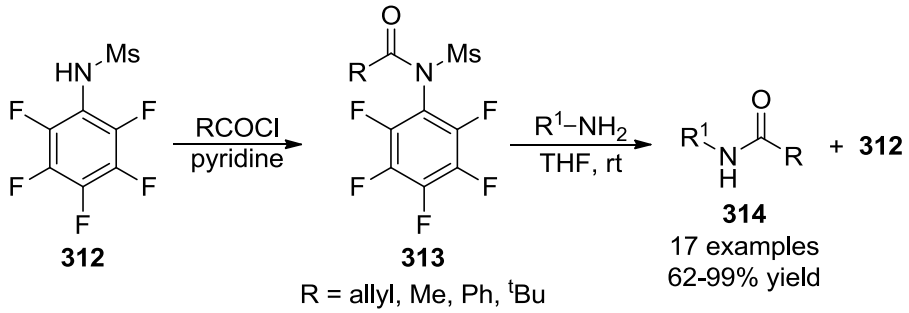
Kikugawa and co-workers showed that *N*-methoxydiacetamide (**305**), synthesised from methoxyamine (**304**) and acetic anhydride, is a highly chemoselective *N*-acylating agent (Scheme 63a). It was found that primary amines were *N*-acetylated over both secondary amines and alcohols, whereas acetic anhydride can acetylate all of these functionalities.[178] The *N*-methoxyacetamide (**307**) formed during the acylation reaction could be removed from the reaction mixture by washing with water. The same group subsequently developed bench stable *N*-(diethylcarbomyl)-*N*-methoxyformamide (**309**) as a selective *N*-formylating agent (Scheme 63b).[179] Atkinson *et al*. subsequently showed that related 3-diacylaminoquinazolinones could also be used as acylating agents for secondary amines.[180]



Scheme 63. a) *N*-Acylation of primary amines using *N*-methoxydiacetamide (**305**) and b) *N*-formylation of primary amines using *N*-(diethylcarbomyl)-*N*-methoxyformamide (**309**).[178-179]

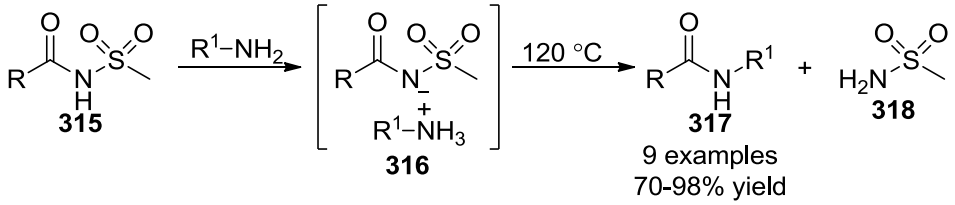
Murakami *et al*. have developed a number of acylating agents based upon substituted anilines. Firstly, 2-(trifluoromethyl)-*N*,*N*-diacetylaniline was shown to be a highly chemoselective acylating agent for primary amines over secondary amines.[181] The introduction of an *N*-mesyl group increased the reactivity of the *ortho*-substituted anilines and allowed the selective

benzoylation of primary amines.[182] Finally, a range of stable *N*-acyl-*N*-(2,3,4,5,6-pentafluorophenyl)methanesulfonamides (**313**) was shown to be highly active *N*-acylating agents, reacting with both primary and secondary amines to form the corresponding amides (**314**) in high yields (Scheme 64).[183] However, the leaving group (**312**) had to be removed from the reaction mixtures *via* column chromatography.



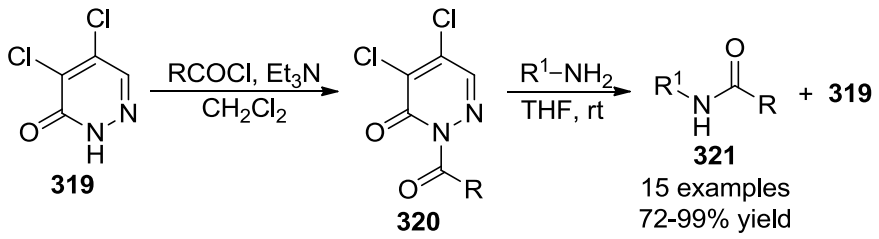
Scheme 64. *N*-Acyl-*N*-(2,3,4,5,6-pentafluorophenyl)methanesulfonamides (**313**) as reactive *N*-acylating agents.[183]

Coniglio *et al*. have shown that primary amines can be *N*-acylated through the condensation of acyl methanesulfonamide ammonium salts (**316**). The salts (**316**), formed from the amine and the *N*-acyl-methanesulfonamide (**315**), were heated at 120 °C to effect the condensation (Scheme 65). The methodology was shown to allow chemoselective *N*-acylation of primary amines over secondary amines as well as for the selective *N*-acylation of amino alcohols.[184]



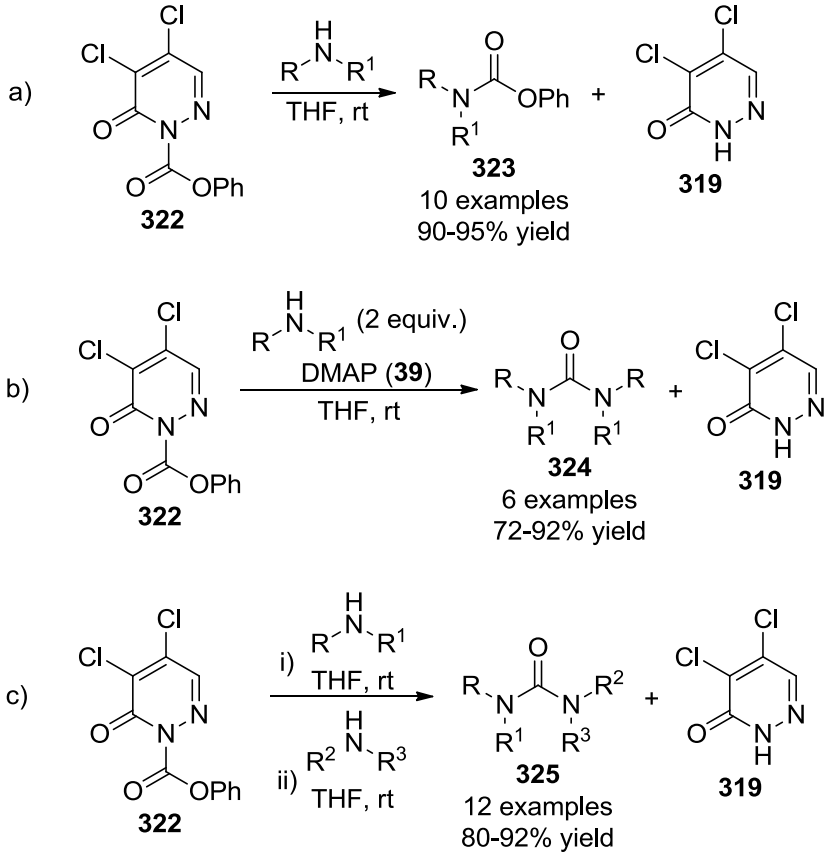
Scheme 65. Chemoselective *N*-acylation through the condensation of *N*-acyl methanesulfonamide ammonium salts (**316**).[184]

Yoon *et al*. have shown that air stable 2-acyl-4,5-dichloropyridazin-3-ones (**320**) are effective *N*-acylating agents for a range of primary amines including amino alcohols (Scheme 66). The parent 4,5-dichloropyridazin-3-one (**319**) can be recovered and re-used, although it needs to be isolated from the crude reaction mixture by column chromatography.[185]



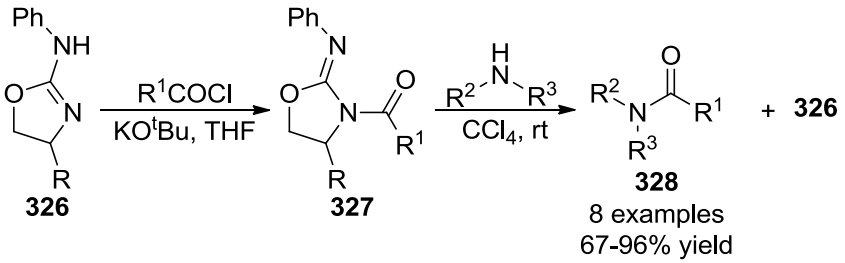
Scheme 66. *N*-acylation of amines using 2-acyl-4,5-dichloropyridazin-3-ones (**320**).[185]

Yoon *et al*. then extended their methodology to the synthesis of carbamates and ureas using the more reactive carbamate derivative **322** of 4,5-dichloropyridazin-3-one (**319**). Treatment of **322** with one equivalent of a primary or secondary amine gave the corresponding carbamates (**323**) in high yields (Scheme 67a), whilst treatment with two equivalents of amine and an equivalent of DMAP (**39**) resulted in the formation of symmetrical ureas (**324**) (Scheme 67b). Unsymmetrical ureas (**325**) could be made in good yields through the sequential addition of two different amines (Scheme 67c).[186]



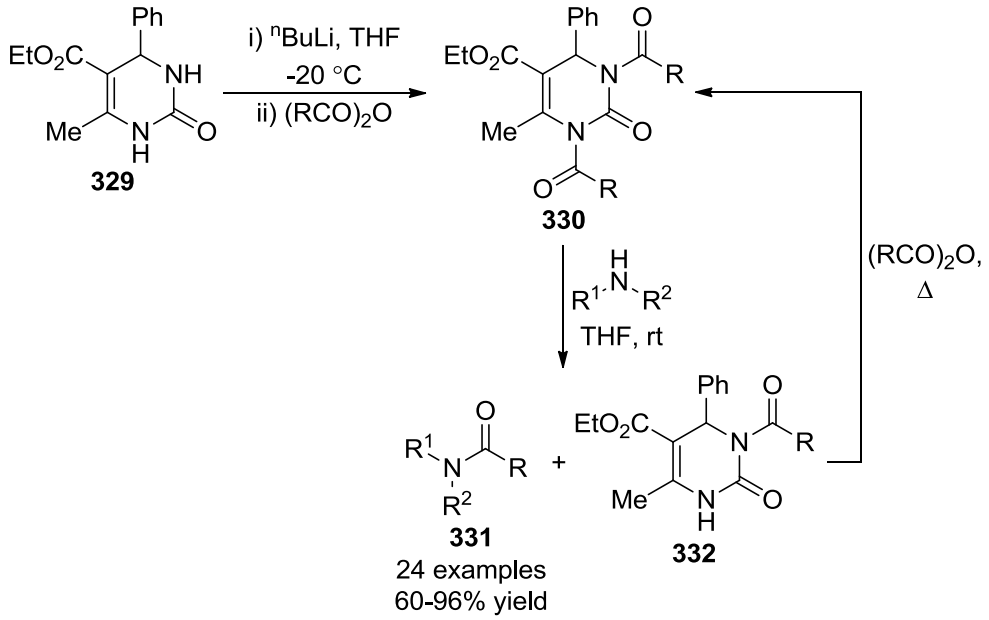
Scheme 67. The use of 4,5-dichloropyridazin-3-one carbamate (**322**) for the synthesis of a) carbamates (**323**), b) symmetrical ureas (**324**), and c) unsymmetrical ureas (**325**).[186]

Kim and co-workers showed that *N*-acyl-2-methylamino-2-thiazolines were reasonable acylating agents for primary amines.[187] The group subsequently found that *N*-acyl-2-phenylimino-oxazolidines (**327**) were more active acylating agents towards a number of amines. The acylating agents (**327**) gave good yields of amides (**328**) when reacted with primary and secondary amines as well as amino alcohols (Scheme 68). With diamines, it was found that the less sterically hindered amine was acylated in all cases. The 2-phenylamino-2-oxazoline (**326**) leaving group could be recovered by washing the reaction mixture with aqueous acid.[188]



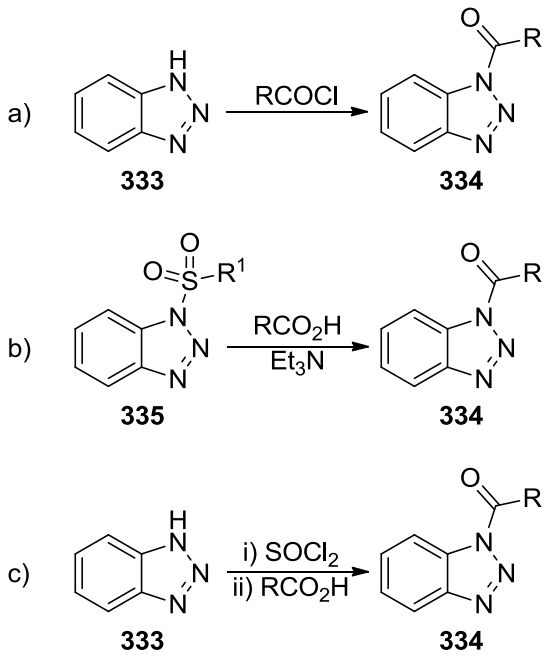
Scheme 68. *N*-acylation using *N*-acyl-2-phenylimino-oxazolidines (**327**).[188]

Recently, Singh *et al*. have shown that *N*1,*N*3-diacyl-3,4-dihydropyrimidin-2(1*H*)-ones (**330**) are efficient acylating agents for ammonia, primary and secondary amines to give primary, secondary, and tertiary amides (**331**) in high yields (Scheme 69). The *N*3-acyl-3,4-dihydropyrimidin-2(1*H*)-one (**322**) leaving group, recovered from the reaction mixtures by column chromatography, could be recycled by heating at reflux with an acid anhydride.[189]



Scheme 69. The use of *N*1,*N*3-diacyl-3,4-dihydropyrimidin-2(1*H*)-ones (**330**) for the synthesis of primary, secondary, and tertiary amides (**331**).[189]

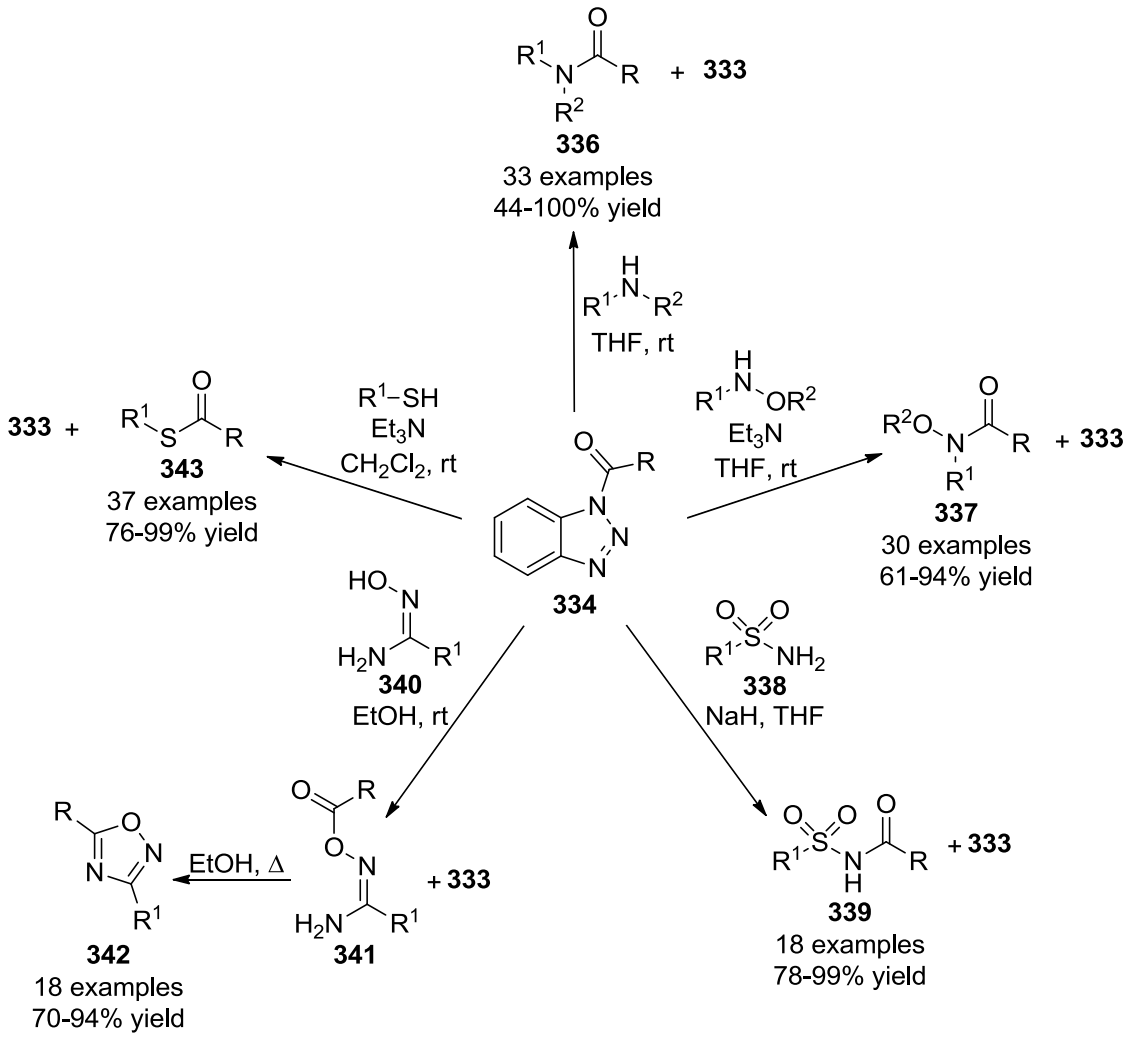
Katritzky and co-workers have extensively researched the use of *N*-acyl benzotriazoles (**334**) as stoichiometric acylating agents. The group has synthesised a vast number of crystalline and stable *N*-acyl benzotriazoles (**334**) over the past 15 years and has applied them to the acylation of many different nucleophiles. The *N*-acyl benzotriazoles (**334**) can be synthesised from benzotriazole (**333**) and an acyl chloride (Scheme 70a) or, can be synthesised from the corresponding acids using either *N*-sulfonylbenzotriazoles (**335**) (Scheme 70b) or thionyl chloride (Scheme 70c). This development allowed *N*-acyl benzotriazoles (**334**) to be synthesised directly from acids whose corresponding acyl chlorides are unstable or unknown.[190-193]



Scheme 70. Synthesis of *N*-acylbenzotriazoles (**334**) from a) acyl chlorides, b) acids using *N*-sulfonylbenzotriazoles (**335**), and c) acids using thionyl chloride.[190-193]

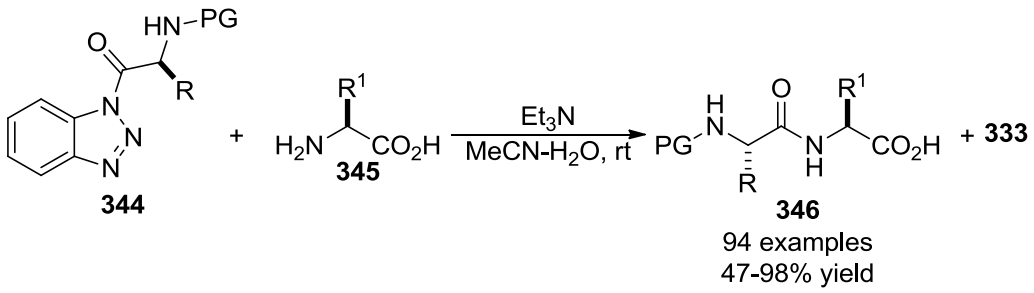
Selected examples of the use of *N*-acyl benzotriazoles (**334**) are shown in Scheme 71 below. Katritzky and co-workers showed that *N*-acyl benzotriazoles (**334**) react quickly with ammonia, primary and secondary amines to form primary, secondary, and tertiary amides (**336**) in high yields.[164] The benzotriazole (**333**) by-product can be removed from the crude reaction mixtures by washing with an aqueous base. *N*-Acyl benzotriazoles (**334**) were also shown to react with *N*,*O*-dimethylhydroxylamine hydrochloride and other *N*-substituted hydroxylamines to form Weinreb amides (**337**, $R^1 = R^2 = Me$) and hydroxamic acids (**337**, $R^2 = H$) in good yields.[194-195] A number of deprotonated sulfonamides (**338**) could also be acylated to form *N*-acyl sulfonamides (**339**), which are a common motif in many drug-like molecules.[196] *N*-Acyl benzotriazoles (**334**) have also been shown to be efficient *O*-acylating agents. For example, they react with amidoximes (**340**) in ethanol at room temperature to form *O*-acylated derivatives

(**341**), which cyclise upon heating to form the corresponding 1,2,4-oxadiazole rings (**342**).[197] *S*-Acylations are also possible by reacting thiols with *N*-acyl benzotriazoles (**334**), with a number of thioesters (**343**) formed in good isolated yield.[198]



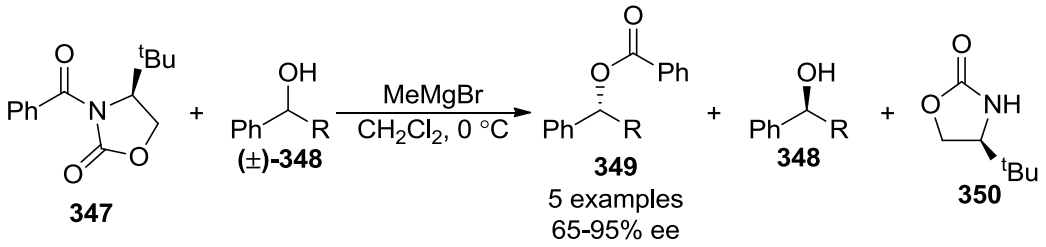
Scheme 71. Selected examples of the uses of *N*-acylbenzotriazoles (**334**).[164,194-198]

More recently, Katritzky and co-workers have focused on the use of the *N*-acyl benzotriazole derivatives of amino acids (**344**) for the syntheses of polypeptides. *N*-Protected amino acids can be converted into air-stable benzotriazole derivatives without racemisation of their stereocentres and these *N*-acyl benzotriazoles (**344**) have been shown to be efficient intermediates for both *N*- and *O*-aminoacylation.[199-200] For example, Katritzky and co-workers synthesised 36 *N*-protected *N*-aminoacyl benzotriazole derivatives (**344**), consisting of 18 natural amino acids variants protected with either Fmoc, Cbz, and Boc, and reacted them with free amino acids (**345**) to give 94 different dipeptides (**346**) in generally good yields (Scheme 72).[201]



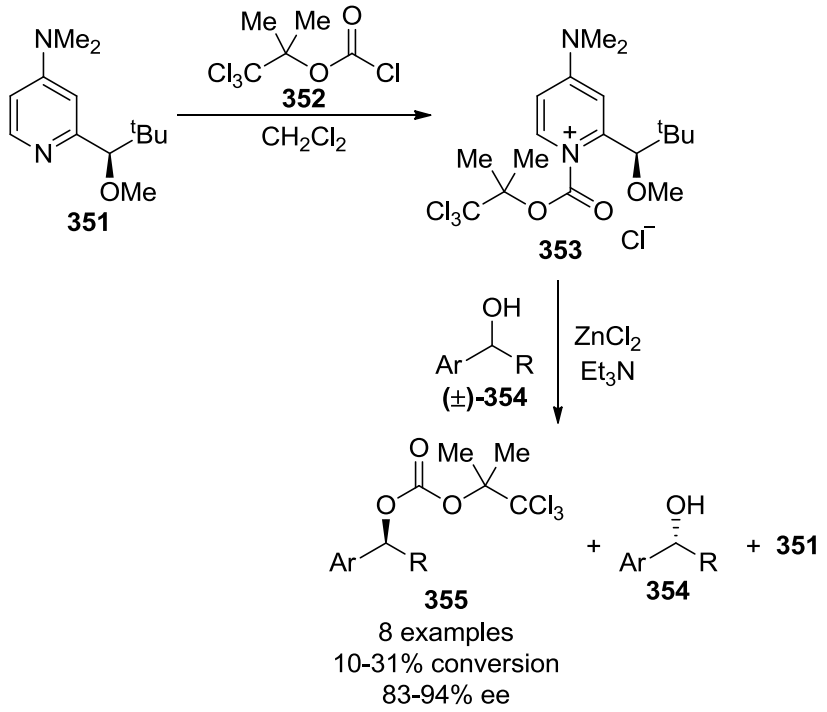
Scheme 72. Synthesis of dipeptides (**346**) using *N*-protected *N*-aminoacyl benzotriazoles (**344**).[201]

There are also a few examples of enantiomerically pure stoichiometric acylating agents that have been used for the kinetic resolution of both alcohols and amines. Evans and co-workers were the first to use an enantiomerically pure acylating agent for the kinetic resolution of secondary alcohols. *N*-Benzoyl oxazolidinone (**347**) was found to acylate enantioselectively a small range of bromomagnesium alkoxides of secondary alcohols (**348**) (Scheme 73). The ester products (**349**) were isolated from unreacted alcohol (**348**) and the oxazolidinone (**350**) by-product *via* column chromatography, giving the esters (**349**) in up to 95% ee.[202]



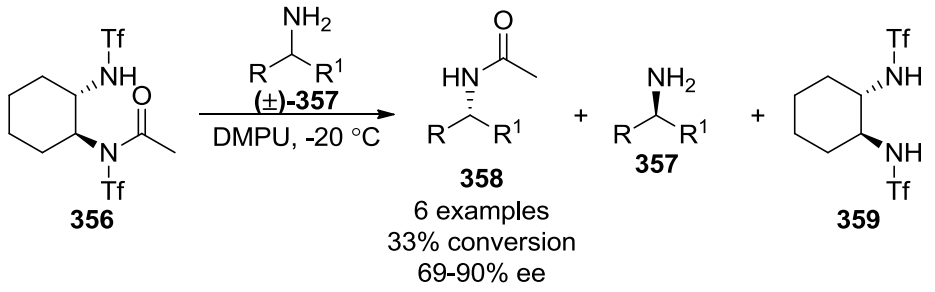
Scheme 73. Kinetic resolution of secondary alcohols (**348**) using oxazolidinone **347**.[202]

Vedejs and Chen showed that enantiomerically pure *N*-acyl DMAP derivative (**353**), made *in situ* from the chiral DMAP **351** and chloroformate **352**, could also be used for the kinetic resolution of secondary alcohols (**354**) (Scheme 74). The acylation requires the use of zinc chloride as a Lewis acid to be effective, although reaction times are slow (40-68 hours) to give modest conversions (10-31%) to carbonate (**355**) in up to 94% ee. As with Evans' methodology, the DMAP leaving group **351** is recovered from the reaction mixture by column chromatography.[203]



Scheme 74. Kinetic resolution of secondary alcohols (**354**) using enantiomerically pure DMAP derivative **353**.[203]

Murakami *et al*. were the first to attempt the kinetic resolution of secondary amines using an enantiomerically pure stoichiometric acyl transfer agent. A chiral version of the *N*,*N*-diacetylanilines previously used for the *N*-acylation of secondary amines (2-acetylamino-2'-diacetylamino-1,1'-binaphthyl) was shown to acylate a small number of racemic secondary amines, although the enantioselectivity was only modest with up to 48% ee observed.[204] Wagner and co-workers subsequently found that enantiomerically pure *N*-acyl sulfonamide **356** was a more effective *N*-acylating agent for the kinetic resolution of secondary amines (**357**), with up to 90% ee obtained for the amide products (**358**) (Scheme 75).[205]

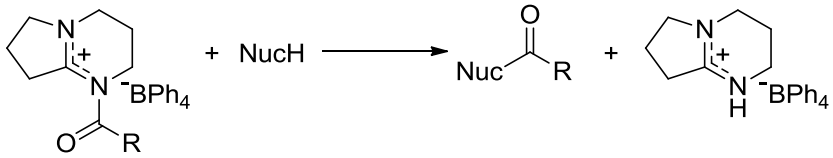


Scheme 75. Kinetic resolution of secondary amines using *N*-acyl sulfonamide **356**.[205]

However, the use of enantiomerically pure stoichiometric acylating agents for the kinetic resolution of alcohols and amines has been superseded by the development of many highly efficient and selective catalytic methods using achiral anhydrides as acyl sources.[37,206-209]

3.1.3 *N*-Acyl DBN·BPh$_4$ Salts as Stoichiometric Acyl Transfer Agents

The isolation of the crystalline and air stable *N*-benzoyl DBN·BPh$_4$ (**275**) salt prompted us to investigate *N*-acyl DBN·BPh$_4$ salts as potential alternatives to acyl chlorides and acid anhydrides in acylation reactions (Scheme 76). It was hoped that a number of crystalline *N*-acyl DBN salts could be synthesised in the same way as *N*-benzoyl DBN·BPh$_4$ (**275**) and that the mild nature and stability of the salts would provide an attractive alternative to using acyl chlorides in acylation reactions. The *N*-acyl DBN salts would also avoid the generation of HCl during acylations that occurs when using acyl chlorides, potentially allowing acid sensitive substrates to be acylated. It was also hoped that the DBN·HBPh$_4$ by-product could be removed by aqueous washes of the crude reaction mixture, giving pure acylated products without the need for column chromatography.



Scheme 76. The potential use of *N*-acyl DBN salts as stoichiometric acylating agents for a range of nucleophiles.

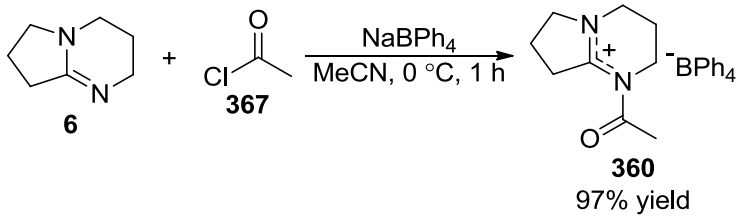
3.2 Results and Discussion

For *N*-acyl DBN·BPh$_4$ salts to be practically useful alternatives to acyl chlorides a wide range of stable salts would need to be readily accessible. Therefore, a number of *N*-acyl DBN·BPh$_4$ salts were synthesised using the same method as for the original *N*-benzoyl DBN·BPh$_4$ (**275**) salt in order to assess their stability, with the results summarised in Table 7 (page 80).[142]

3.2.1 Synthesis of *N*-Acyl DBN·BPh$_4$ Salts

Firstly, an *N*-acetyl DBN·BPh$_4$ salt (**360**) was synthesised by adding DBN (**6**) dropwise to a solution of acetyl chloride (**367**) and sodium tetraphenylborate in acetonitrile at 0 °C and stirring for one hour (Scheme 77). During this time a white precipitate of sodium chloride forms, which is removed by filtering the reaction mixture through a pad of Celite®, before the solution is then concentrated under reduced pressure to give an off-white solid. The solid was successfully recrystallised from dichloromethane and hexane to give the *N*-acetyl DBN·BPh$_4$

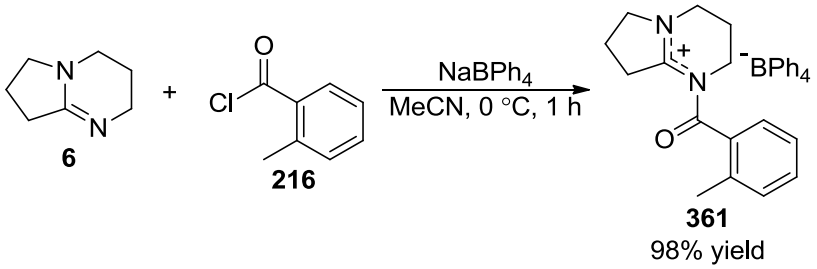
salt (**360**) as large transparent plates in 97% yield. This salt (**360**) was stable and could be stored in an atmosphere of air without any decomposition being observed.



Scheme 77. Synthesis of *N*-acetyl DBN·BPh$_4$ (**360**).

The structure of the *N*-acetyl DBN·BPh$_4$ salt (**360**) was confirmed by ^{1}H NMR spectroscopic analysis in deuterated dichloromethane, which showed a slight downfield shift of the resonances of the DBN protons and the appearance of the acetyl peak at δ = 2.02 ppm. High resolution mass spectrometry showed a single peak at *m*/*z* 167.1277 corresponding to the molecular weight of the positively charged *N*-acetyl DBN ion. The downfield shifts in the ^{1}H NMR spectrum of the signals for the DBN protons adjacent to the positively charged nitrogen atoms were less than those observed previously for the *N*-benzoyl DBN·Cl (**269**) salt. This could be due to increased shielding by the tetraphenylborate counter-ion compared with the chloride counter-ion, or could be due to the fact that less polar deutrated dichloromethane was used as an NMR solvent for the tetraphenylborate salt, whilst the more polar deuterated chloroform was used for the chloride salt.

Next, DBN (**6**) was added to a solution of *o*-toluoyl chloride (**216**) and sodium tetraphenylborate in acetonitrile to see if more sterically demanding *N*-benzoyl DBN·BPh$_4$ derivatives could be formed. Pleasingly, the reaction worked well to afford *N*-*o*-toluoyl DBN·BPh$_4$ (**361**) in 98% yield after recrystallisation (Scheme 78). ^{1}H NOE spectroscopic



Scheme 78. Synthesis of *N*-*o*-toluoyl DBN·BPh$_4$ (**361**).

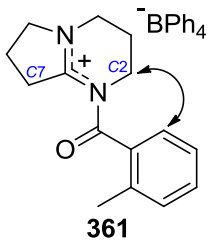
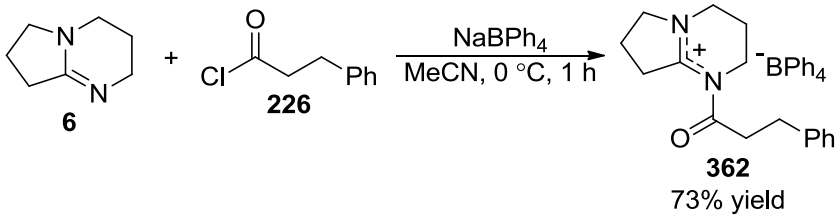


Figure 10. Observed ^{1}H NOE interaction between the tolyl and DBN rings.

analysis of salt **361** showed an interaction between its *ortho*-proton and the *C*2 protons of the DBN ring, whilst no interaction was observed with the *C*7 DBN protons (Figure 10). This suggests a conformational preference for salt **361** in solution in which the tolyl ring is angled with its *ortho*-proton pointing towards the six-membered ring of the DBN fragment.

The salt forming methodology was then applied to the synthesis of *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**) from hydrocinnamoyl chloride (**226**) (Scheme 79). The crude solid from the reaction was successfully recrystallised from dichloromethane and hexane to give *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**) as white plates in a 73% yield. The ^{1}H NMR spectrum of the salt was consistent with the spectra observed for the previous salts, with the molecular ion of *m*/*z* 257.1643 being present in the high resolution mass spectrum.



Scheme 79. Synthesis of *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**).

An X-ray crystal structure of *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**) (Figure 11) was obtained to look at the differences, if any, between its *N*-alkyl side chain and the structure of the *N*-benzoyl DBN·BPh$_4$ (**275**) structure obtained previously (Figure 8, page 59). The crystal structure of salt **362** shows that the positive charge is delocalised over both nitrogen atoms with a N1-C8 bond length of 1.356 Å and a N2-C8 bond length of 1.304 Å, which are similar in length to those observed previously for the *N*-benzoyl salt. However, the carbonyl of salt **362** lies in the same plane as the delocalised amidine system, whereas the carbonyl of the *N*-benzoyl salt (**275**) lies 36.1° out of the plane. This could be due to increased delocalisation of the amidine onto the carbonyl in the *N*-hydrocinnamoyl salt compared with the *N*-benzoyl salt, however the N1-C1 bond lengths in both X-ray crystal structures are longer than would be expected if there were significant delocalisation (1.429 Å for the *N*-hydrocinnamoyl salt and 1.419 Å for the *N*-benzoyl salt). The carbonyl stretching frequencies observed in the infrared spectra of the two salts are comparable with each other, with ν_{max} = 1742 cm^{-1} for *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**) and ν_{max} = 1714 cm^{-1} for *N*-benzoyl DBN·BPh$_4$ (**275**). These frequencies are higher than those found in tertiary amides, which suggests that there is decreased delocalisation of the nitrogen lone pair into the π-system of the carbonyl in the *N*-acyl DBN·BPh$_4$ salts. Therefore, the coplanar

carbonyl and amidine ring in the X-ray structure of *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**) is possibly an artefact of crystallisation.

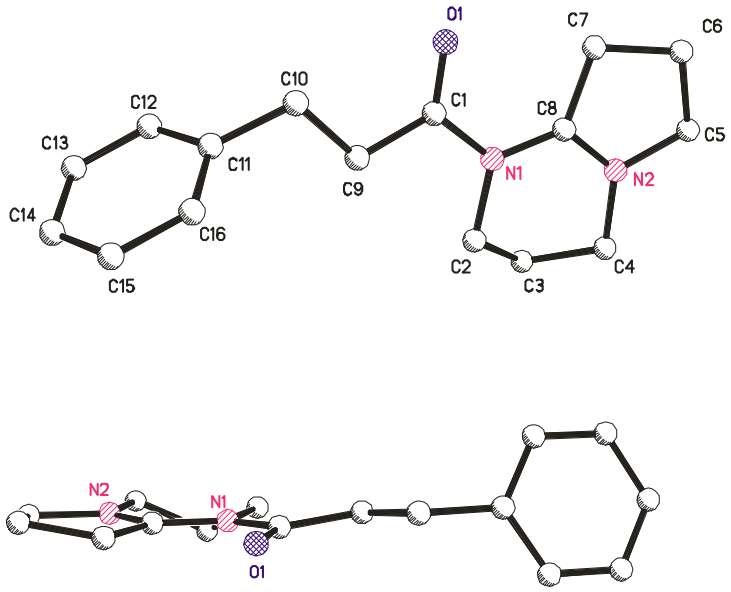
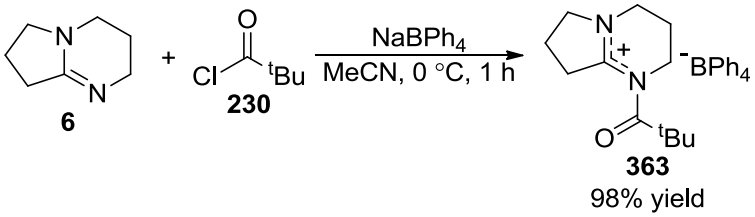


Figure 11. X-ray crystal structure of *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**). Tetraphenylborate counter-ion not shown for clarity.

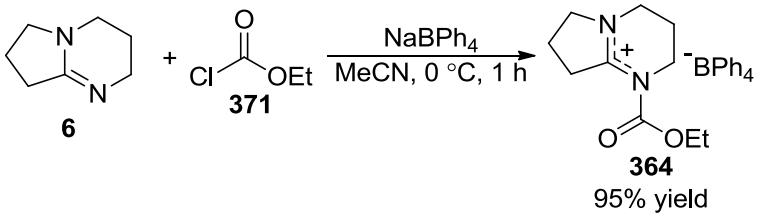
Next, DBN (**6**) was added to a solution of the sterically demanding pivaloyl chloride (**230**) and sodium tetraphenylborate in acetonitrile to form the corresponding *N*-pivaloyl DBN·BPh$_4$ salt (**363**) (Scheme 80). The crude solid obtained from the reaction was purified by recrystallisation from dichloromethane and hexane to give *N*-pivaloyl DBN·BPh$_4$ (**363**) as small white crystals in 98% yield. High resolution mass spectrometry confirmed the presence of the molecular ion of salt **363** and the ^{1}H NMR spectrum showed the distinctive *tert*-butyl peak at δ = 1.34 ppm.



Scheme 80. Synthesis of *N*-pivaloyl DBN·BPh$_4$ (**363**).

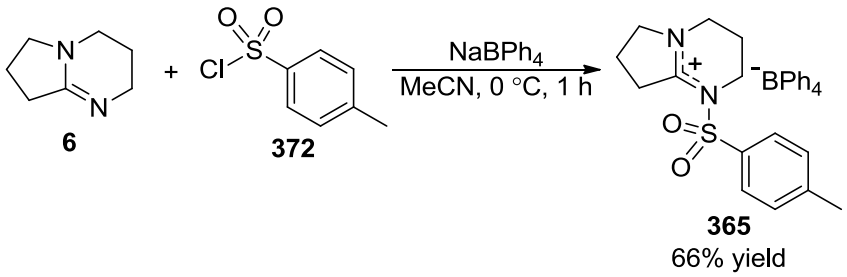
As *N*-acyl DBN·BPh$_4$ salt formation from aromatic, straight chain, and bulky acyl chlorides had been successful it was decided to investigate the use of more reactive acyl, sulfonyl, and phosphoryl chlorides to see if bench stable alternatives could be made for use in acylation reactions. Pleasingly, reaction with ethyl chloroformate (**371**) proceeded smoothly to form the

N-ethyl carboxyl DBN·BPh$_4$ salt (**364**) in 95% yield after recrystallisation (Scheme 81). The salt was isolated as an air stable white powder, unlike the parent ethyl chloroformate (**371**) that decomposes upon contact with moisture in the air.



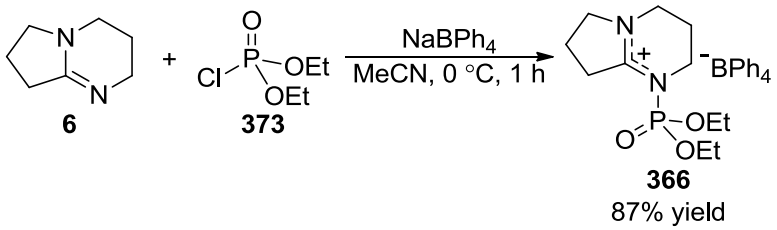
Scheme 81. Synthesis of *N*-ethyl carboxyl DBN·BPh$_4$ (**364**).

Next, the salt formation methodology was applied to *p*-toluenesulfonyl chloride (**372**) in an attempt to synthesise a bench stable sulfonylating agent. As hoped, the reaction formed an air stable *N*-*p*-toluenesulfonyl DBN·BPh$_4$ salt (**365**), albeit in a reduced 66% yield after recrystallisation (Scheme 82). As for the other *N*-acyl DBN salts, the ^{1}H NMR spectrum of salt **365** showed the characteristic downfield shifts of the DBN ring protons and the molecular ion for salt **365** was detected by high resolution mass spectrometry.



Scheme 82. Synthesis of *N*-*p*-toluenesulfonyl DBN·BPh$_4$ (**365**).

The highly reactive diethyl phosphoryl chloride (**373**) also formed its corresponding salt (**366**) in the presence of DBN (**6**) and sodium tetraphenylborate (Scheme 83). The *N*-diethyl phosphoryl DBN·BPh$_4$ (**366**) salt was isolated as a white powder after recrystallisation in an 87% yield. High resolution mass spectrometry confirmed the presence of the salt molecular ion, whilst the ^{31}P{^{1}H} NMR spectrum showed a single peak at δ = -1.70 ppm. The *N*-diethyl phosphoryl DBN·BPh$_4$ (**366**) is much easier to handle than its parent phosphorylchloride (**373**), which rapidly decomposes in air, and may prove to be a useful reagent for phosphorylation reactions.



Scheme 83. Synthesis of *N*-diethyl phosphoryl DBN·BPh$_4$ (**366**).

The results from all of the *N*-acyl DBN·BPh$_4$ salt formations are summarised in Table 7 overleaf. All of the salts synthesised are crystalline solids that could potentially be synthesised on a large scale.

For example, *N*-benzoyl DBN·BPh$_4$ (**275**) was synthesised on a 15 mmol scale forming 7.62 g of crystalline product. The salts are bench stable and can be stored and handled in air without decomposition.[‡] This is in contrast to many of the acyl chlorides used, especially acetyl chloride (**367**), ethyl chloroformate (**371**), *p*-toluenesulfonyl chloride (**372**), and diethyl phosphoryl chloride (**373**), which are all water sensitive and decompose rapidly to release HCl gas upon contact with moisture in the air. The ease of synthesis and the favourable properties of these *N*-acyl DBN·BPh$_4$ salts could potentially make them valuable alternatives to acyl chlorides in acylation reactions.

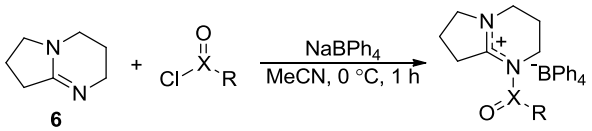
3.2.2 Synthesis of the *N*-Acyl DBN·BPh$_4$ Salt of an Amino Acid

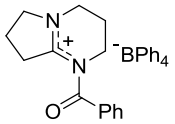
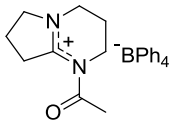
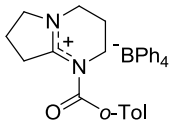
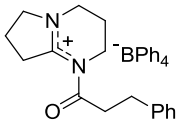
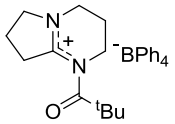
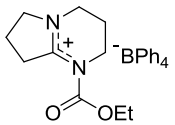
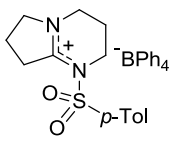
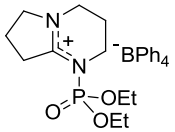
As a variety of achiral *N*-acyl DBN·BPh$_4$ salts had been successfully synthesised, it was decided to try and form an enantiomerically pure *N*-acyl DBN·BPh$_4$ salt of an amino acid derivative, which could have potential applications for the synthesis of peptides. However, the synthesis of an amino acid derived salt was predicted to be more challenging than the syntheses of previous *N*-acyl salts. Acyl chlorides of amino acids are often unstable and a suitable nitrogen protecting group has to be used. In addition, the basic DBN (**6**) used for salt formation could deprotonate the acidic α-proton of the amino acid derivative, leading to racemisation of the α-stereocentre.

Initial attempts at forming the acyl chloride of *N*-Boc protected phenylalanine using oxalyl chloride were unsuccessful. Analysis of the reaction mixture by ^{1}H NMR and high resolution mass spectrometry showed complete decomposition of the amino acid, with no evidence of acyl

[‡] At the time of writing, a sample of *N*-benzoyl DBN·BPh$_4$ (**275**) had been stored for 11 months in air without any decomposition occurring.

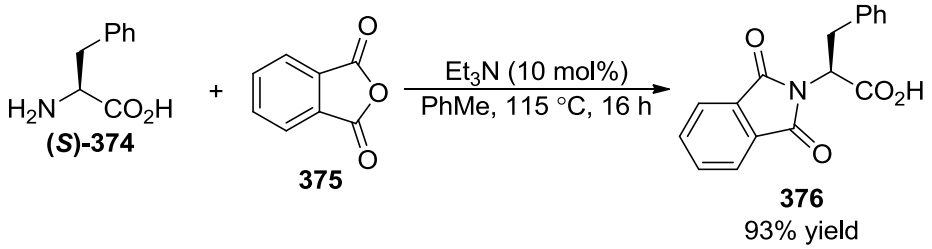
Table 7. Synthesis of *N*-acyl DBN·BPh$_4$ salts.



Entry	*N*-Acyl DBN·BPh$_4$	Yield (%)[a]	Form	mp (°C)
1	 **275**	93	White needles	117-119
2	 **360**	97	Transparent plates	185[b]
3	 **361**	98	White crystals	173-176
4	 **362**	73	White plates	167-170
5	 **363**	98	White crystals	157-158
6	 **364**	95	White powder	156-157
7	 **365**	66	Beige powder	185[b]
8	 **366**	87	White powder	132-135

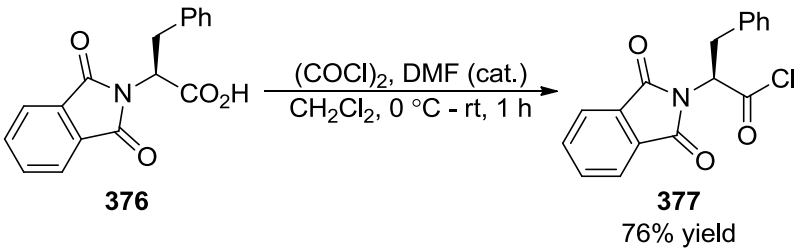
[a]Isolated yields by recrystallisation from CH_2Cl_2 and hexane. [b]Decomposition observed.

chloride formation. Therefore, it was decided to investigate the use of a phthalate protecting group instead of the Boc protecting group. L-Phenylalanine (**374**) was protected by heating with phthalate anhydride (**375**) and triethylamine in toluene under Dean-Stark conditions for 16 hours (Scheme 84).[210] The crude product was recrystallised from hot ethanol and water to give *N*-phthaloyl-L-phenylalanine (**376**) in 93% yield, with the spectroscopic data in accordance with that reported in the literature.



Scheme 84. Synthesis of phthalate protected L-phenylalanine (**376**).

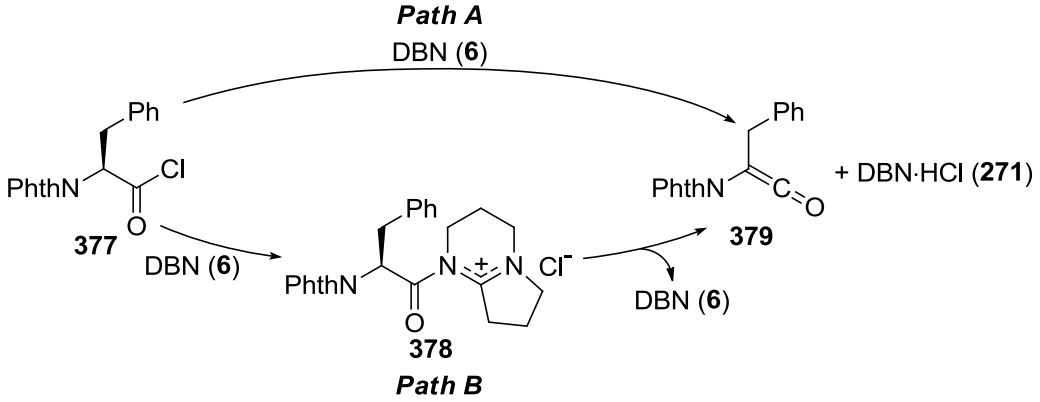
Next, *N*-phthaloyl-L-phenylalanine (**376**) was converted into its corresponding acyl chloride (**377**) using oxalyl chloride and a catalytic amount of DMF (Scheme 85).[211] The crude product was purified by recrystallisation from dichloromethane and hexane to give the *N*-phthaloyl-L-phenylalanine acyl chloride (**377**) in 76% yield. The ^{1}H NMR spectrum showed the disappearance of the broad acid proton resonance at δ = 8.61 ppm of the starting material and was consistent with the previously reported data.



Scheme 85. Synthesis of the acyl chloride of phthalate protected L-phenylalanine (**377**).

The *N*-phthaloyl-L-phenylalanine acyl chloride (**377**) was then reacted with DBN (**6**) in the presence of sodium tetraphenylborate under the standard salt forming conditions. After stirring at 0 °C for one hour the reaction was worked-up to give a yellow oil. ^{1}H NMR spectroscopic analysis of the crude oil showed that the starting material had been consumed, but the spectrum was inconsistent with *N*-acyl DBN salt formation. High resolution mass spectrometry and ^{1}H NMR spectrum analysis showed that the major species in the crude was in fact protonated DBN

as its tetraphenylborate salt.[§] Further inspection of the ^{1}H NMR spectrum showed that the distinctive doublet of doublets usually observed for the α-proton of the amino acid (which appears at δ = 5.25 ppm in acyl chloride **377**) was missing. This suggests that the amino acid fragment is being decomposed by deprotonation of its α-proton either directly from the acyl chloride (**377**) (Scheme 86, Path A) or from any *N*-acyl DBN (**378**) that does form (Scheme 86, Path B). The ketene species formed (**379**) would be highly reactive and explains the decomposition of the acyl chloride (**377**) observed. The deprotonation would initially form DBN hydrochloride (**271**), which then exchanges its chloride counter-ion with the sodium tetraphenylborate to explain the presence of DBN hydrotetraphenylborate in the crude reaction mixture.

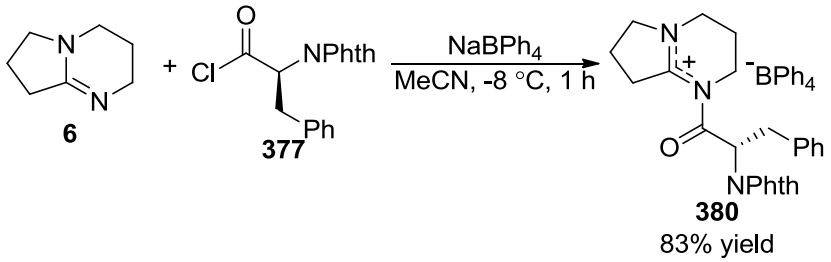


Scheme 86. Possible decomposition pathways of *N*-phthaloyl-L-phenylalanine acyl chloride (**377**).

In an attempt to prevent decomposition of *N*-phthaloyl-L-phenylalanine acyl chloride (**377**) through deprotonation the salt formation conditions were modified. The reaction was diluted by a factor of two with acetonitrile and cooled to -8 °C rather than 0 °C before the DBN (**6**), also diluted in acetonitrile, was added dropwise over an extended period of time (Scheme 87). After stirring at -8 °C for one hour, the precipitate of sodium chloride was removed *via* filtration through Celite® before the solution was concentrated under reduced pressure to give a yellow solid. Pleasingly, the molecular ion of the desired salt **380** was detected by high resolution mass spectrometry. Importantly, the ^{1}H NMR spectrum showed the characteristic α-proton as a doublet of doublets at δ = 5.55 ppm. The chemical shifts in the ^{1}H NMR spectrum for the DBN ring protons were consistent with those observed for other *N*-acyl DBN salts, but the peaks showed increased splitting presumably due to their diastereotopic nature from the chiral centre

[§] A pure sample of DBN hydrotetraphenylborate was obtained and characterised through recrystallisation of the crude reaction mixture.

of the amino acid fragment. The *N*-Phth-Phe DBN·BPh$_4$ salt (**380**) had a specific optical rotation of -11.2 ° (*c* = 1.25 g/100 mL in MeCN) showing that the stereocentre had not been completely racemised. The exact enantiomeric excess was later determined by reacting *N*-Phth-Phe DBN·BPh$_4$ (**380**) with (*S*)-phenylalanine methyl ester and analysing the ^{1}H NMR spectrum of the resulting dipeptide (see page 87).



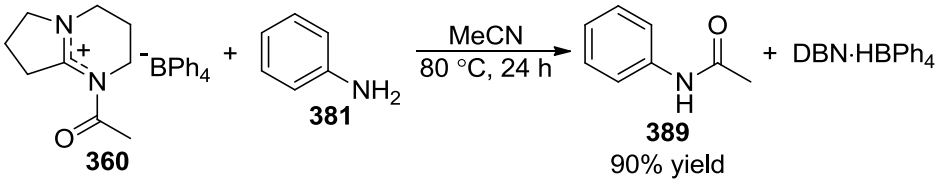
Scheme 87. Synthesis of *N*-Phth-Phe DBN·BPh$_4$ (**380**).

3.2.3 *N*-Acyl DBN·BPh$_4$ Salts for the *N*-Acylation of Amines

The amide bond is ubiquitous throughout nature and is found in many pharmaceutically active molecules, making the *N*-acylation of amines to form amide products one of the most frequently used reactions in drug synthesis.[150] Therefore, due to the synthetic importance of amides, the use of *N*-acyl DBN·BPh$_4$ salts for the acylation of amines to form amides was investigated.

3.2.3.1 *N*-Acylation of Anilines

The acylation of aniline (**381**) using *N*-acetyl DBN·BPh$_4$ (**360**) was the first acylation reaction to be investigated. An initial screen of solvents and conditions revealed that *N*-acetyl DBN·BPh$_4$ (**360**) was only soluble in acetonitrile, dichloromethane, and tetrahydrofuran, and that the reaction with aniline (**381**) in acetonitrile at 80 °C was optimal. Therefore, aniline (**381**) was added to 1.3 equivalents of *N*-acetyl DBN·BPh$_4$ (**360**) in acetonitrile and heated at 80 °C for twenty-four hours, before being cooled to room temperature and concentrated under reduced pressure (Scheme 88). ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed



Scheme 88. Acylation of aniline (**381**) using *N*-acetyl DBN·BPh$_4$ (**360**).

that the reaction had gone to completion with the appearance of the characteristic broad amide proton resonance at δ = 7.89 ppm, as well as the appearance of the acetyl singlet at δ = 2.06 ppm. The reaction mixture was readily purified by dissolving the crude reaction product in ethyl acetate and filtering off the insoluble salts, which are a mixture of remaining *N*-acetyl DBN·BPh$_4$ (**360**) and DBN·HBPh$_4$ that is formed during the reaction. The resulting solution was again concentrated under reduced pressure to give an analytically pure sample of *N*-phenylacetamide (**389**) in 90% yield without the need for column chromatography.

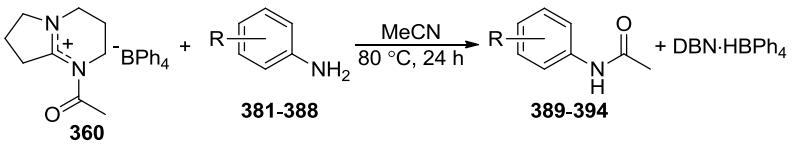
The successful acylation protocol was then applied to a range of anilines (**382**-**388**), with the results summarised in Table 8. The reactions of *N*-acetyl DBN·BPh$_4$ (**360**) with *para*- and *meta*-toluidine (**382** and **383**) worked well, with 100% conversion observed in both cases, enabling the amide products (**390** and **391**) to be isolated after removal of the excess salts by filtration in 94 and 99% yields respectively (Table 8, entries 2 and 3). However, the reaction of more sterically demanding *ortho*-toluidine (**384**) with *N*-acetyl DBN·BPh$_4$ (**360**) was unsuccessful and no amide product was present in the crude ^{1}H NMR spectrum after twenty-four hours (Table 8, entry 4). Increased steric demand in the *para*-position did not affect the reaction, with *p-tert*-butylaniline (**385**) reacting smoothly to give the corresponding amide **392** in 82% isolated yield (Table 8, entry 5). Halogen substitution on the aniline reduced the conversion slightly, with *p*-fluoroaniline (**386**) reacting with *N*-acetyl DBN·BPh$_4$ (**360**) to give 88% conversion into the corresponding amide (**393**) (Table 8, entry 6). The presence of strongly electron-withdrawing or electron-donating groups was less well tolerated in the acylation reaction. No conversion into amide was observed when *p*-nitroaniline (**387**) was used, whilst only 46% conversion into amide **394** was observed in the crude ^{1}H NMR spectrum of the reaction of 3,4-(methylenedioxy)aniline (**388**) (Table 8, entries 7 and 8).

3.2.3.2 *N*-Acylation of Primary Amines

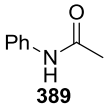
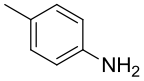
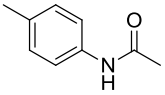
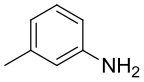
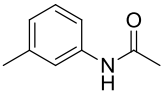
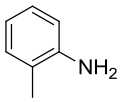
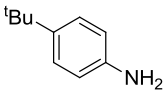
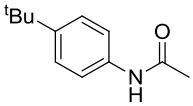
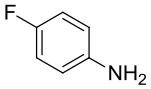
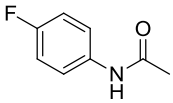
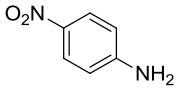
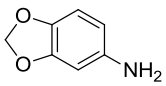
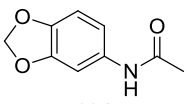
With conditions established for the acylation of anilines and a convenient work-up procedure that enabled pure amide products to be isolated by removal of excess DBN salts by filtration without the need for column chromatography, the acylation of primary amines was investigated.

The acylation of benzylamine (**395**) was used to optimise the acylation of primary amines. As for the acylation of anilines, benzylamine (**395**) was added to a solution of *N*-acetyl DBN·BPh$_4$ (**360**) in acetonitrile and heated at 80 °C (Scheme 89).

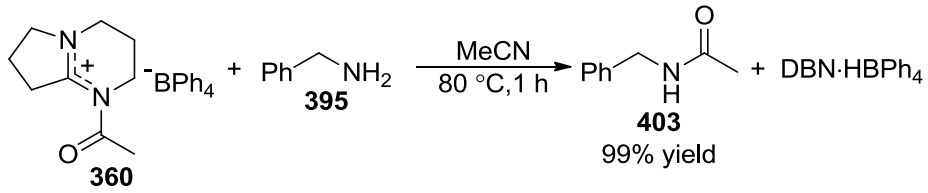
Table 8. Acylation of anilines (**381**-**388**) using *N*-acetyl DBN·BPh$_4$ (**360**).[a]



360 **381-388** **389-394**

Entry	Aniline (**381**-**388**)	Amide (**389**-**394**)	Conversion (%)[b,c]
1	 **381**	 **389**	100 (90)
2	 **382**	 **390**	100 (94)
3	 **383**	 **391**	100 (99)
4	 **384**	-	0 (-)
5	 **385**	 **392**	100 (82)
6	 **386**	 **393**	88 (76)
7	 **387**	-	0 (-)
8	 **388**	 **394**	46 (-)

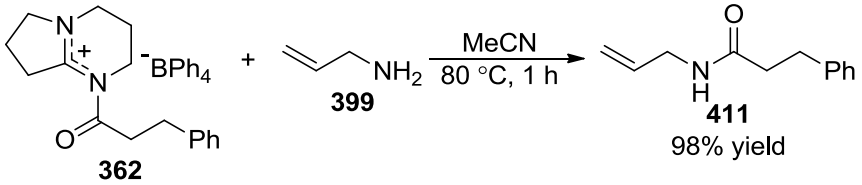
[a]Reactions performed on a 0.5 mmol scale using 0.65 mmol *N*-acetyl DBN·BPh$_4$ (**360**). [b]Determined by ^{1}H NMR spectroscopic analysis. [c]Isolated yields in parentheses.



Scheme 89. Acylation of benzylamine (**395**) using *N*-acetyl DBN·BPh$_4$ (**360**).

Pleasingly, after only one hour ^{1}H NMR analysis showed 100% conversion into *N*-benzylacetamide (**403**), with the appearance of the broad amide proton resonance at δ = 6.08 ppm along with the downfield shift of the doublet due to the benzylic protons, which had moved from δ = 3.75 ppm to δ = 4.30 ppm. The reaction mixture was again purified by dissolving the crude reaction product in ethyl acetate and filtering off the insoluble DBN salts. Concentration of the filtrate under reduced pressure gave an analytically pure sample of *N*-benzylacetamide (**403**) in 99% yield, without the need for column chromatography.

The acylation protocol was then applied to a range of primary amines, the results of which are summarised in Table 9. 2-Phenethylamine (**396**) was successfully acylated using *N*-acetyl DBN·BPh$_4$ (**360**), giving 100% conversion into product (**404**) after one hour (Table 9, entry 2). *N*-Phenethylacetamide (**404**) was isolated by washing the crude reaction product with ethyl acetate to remove insoluble salts. The washing and filtering procedure had to be repeated twice to give a pure sample of *N*-phenethylacetamide (**404**) in 97% yield. The *N*-acylation of piperonylamine (**397**) also proceeded with complete conversion after one hour, leading to the isolation of 70% of the corresponding amide (**405**) (Table 9, entry 3). The *N*-acylations of hexylamine (**398**) and allylamine (**399**) with *N*-acetyl DBN·BPh$_4$ (**360**) proved more difficult (Table 9, entries 4 and 5). Although the crude ^{1}H NMR spectra of both reactions showed 100% conversion, the amide products (**406** and **407**) could not be isolated by the standard washing method. Even after multiple washes and filtrations, ^{1}H NMR spectroscopic analysis of the filtrates still showed the presence of DBN·HBPh$_4$ salts. Attempts to remove these salts by column chromatography were also unsuccessful as they were found to co-elute with the amide

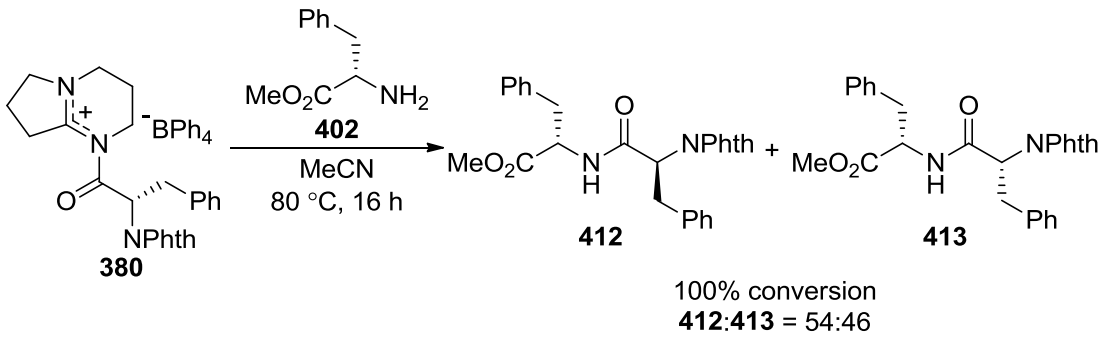


Scheme 90. Acylation of allylamine (**399**) with *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**).

products. However, the acylation of allylamine (**399**) using *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**) instead of *N*-acetyl DBN·BPh$_4$ (**360**) did allow isolation of the amide product (**411**) in high yield (Scheme 90).

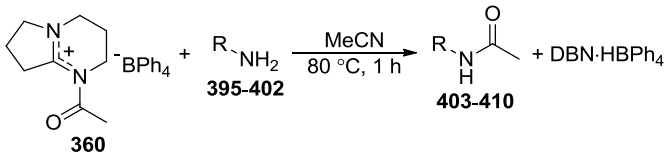
The reaction of sterically demanding *tert*-butylamine (**400**) with *N*-acetyl DBN·BPh$_4$ (**360**) proceeded smoothly, with 70% *N*-(*t*-butyl)acetamide (**408**) isolated after washing the crude with ethyl acetate (Table 9, entry 6). This *N*-acylation methodology was then applied to enantiomerically pure (*R*)-α-methylbenzylamine (**401**), to test whether the α-stereocentre would be racemised under the reaction conditions (Table 9, entry 7). (*R*)-*N*-(1-Phenethyl)acetamide (**409**) was isolated in a 66% yield after one hour with the measured specific rotation of +121 ° (*c* = 0.97 g/100 mL in $CHCl_3$) comparable with the values reported in the literature [$[\alpha]_D^{25}$ = +127, (*c* = 1.0 g/100 mL in CH_2Cl_2)],[212] suggesting that the integrity of the stereocentre had been retained. *N*-Acetyl DBN·BPh$_4$ (**360**) was then used to acylate phenylalanine methyl ester (**402**), giving the corresponding amide (**410**) in quantitative conversion with 99% isolated yield (Table 9, entry 8). The specific rotation of amide **410**, $[\alpha]_D^{18}$ = +84 (*c* = 0.68 g/100 mL in $CHCl_3$) was comparable with the literature value [$[\alpha]_D^{25}$ = +96 (*c* = 1.0 g/100 mL in $CHCl_3$)] and therefore confirmed that little racemisation of the stereocentre of the amino acid had occurred during the reaction.[213]

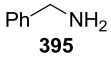
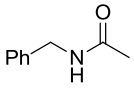
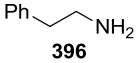
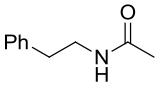
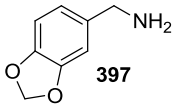
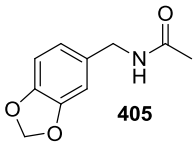
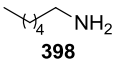
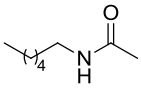
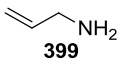
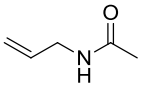
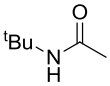
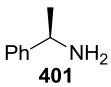
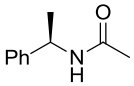
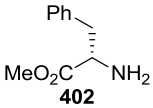
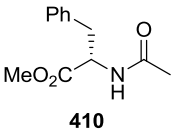
The fact that the acylation of (*S*)-phenylalanine methyl ester (**402**) with *N*-acetyl DBN·BPh$_4$ (**360**) had not led to significant racemisation of the amino acid stereocentre allowed the enantiomeric excess of the *N*-Phth-Phe-DBN·BPh$_4$ salt (**380**) to be determined. The reaction between (*S*)-phenylalanine methyl ester (**402**) and *N*-Phth-Phe-DBN·BPh$_4$ salt (**380**) proceeded smoothly, giving 100% conversion into the corresponding dipeptide. However, ^{1}H and ^{13}C{^{1}H} NMR spectroscopic analysis showed that a mixture of diastereoisomers (**412** and **413**) had been



Scheme 91. Acylation of (*S*)-phenylalanine methyl ester (**402**) using *N*-Phth-Phe-DBN·BPh$_4$ (**380**) forms a mixture of diastereoisomers (**412** and **413**), showing that the stereocentre of salt (**380**) is scalemic.

Table 9. Acylation of primary amines (**395**-**402**) using *N*-acetyl DBN·BPh$_4$ (**360**).[a]

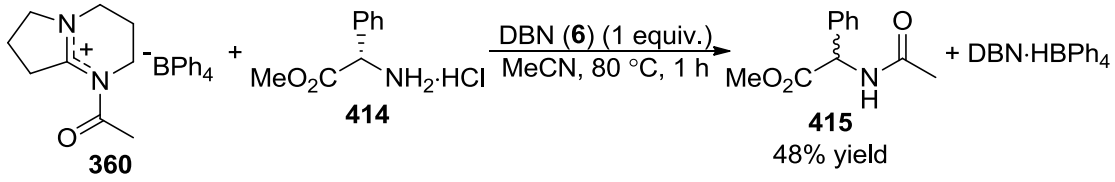


Entry	Amine (**395**-**402**)	Amide (**403**-**410**)	Conversion (%)[b,c]
1	 **395**	 **403**	100 (99)
2	 **396**	 **404**	100 (97)
3	 **397**	 **405**	100 (70)
4	 **398**	 **406**	100 (-)[d]
5	 **399**	 **407**	100 (-)[d]
6	 **400**	 **408**	100 (76)
7	 **401**	 **409**	94 (66)
8	 **402**	 **410**	100 (99)

[a]Reactions performed on a 0.5 mmol scale using 0.65 mmol *N*-acetyl DBN·BPh$_4$ (**360**). [b]Determined by ^{1}H NMR spectroscopic analysis. [c]Isolated yields in parentheses. [d]Amide could not be isolated by removal of excess DBN salts by filtration.

formed in a ratio of 54:46 (Scheme 91). As the stereocentre of (*S*)-phenylalanine methyl ester (**402**) had been shown previously to not undergo racemisation under the acylation conditions, the diastereomeric products (**412** and **413**) must have arisen from a scalemic sample of *N*-Phth-Phe-DBN·BPh$_4$ (**380**). The *N*-Phth-Phe-DBN·BPh$_4$ salt (**380**) is estimated to have 8% ee based upon the integrals of the ^{1}H NMR spectrum of the dipeptide diastereoisomers (**412** and **413**), showing that significant racemisation must have occurred during its formation (Scheme 87, page 83).

The acylation of (*S*)-phenylglycine methyl ester hydrochloride (**414**) with *N*-acetyl DBN·BPh$_4$ (**360**) did lead to partial racemisation of the α-stereocentre of the amide product (**415**) (Scheme 92). An equivalent of DBN (**6**) was added to the reaction to liberate the free amine of (*S*)-phenylglycine methyl ester hydrochloride (**414**), resulting in the formation of the *N*-acyl product **415** in a reduced 48% yield. Without added base the reaction does not proceed, whilst the use of weaker bases such as triethylamine and potassium carbonate gave low conversions into the amide product (10% and 36% respectively). Although the use of an equivalent of DBN (**6**) gave 75% conversion, the specific rotation of the product **415** was measured as +26 ° (*c* = 1.25 g/100 mL in MeOH), which compares with a literature value of +102 ° (*c* = 1.00 g/100 mL in MeOH).[214] This suggests that the acidic α-stereocentre of either the (*S*)-phenylglycine (**414**) or the amide **415** is partially racemised during the course of the reaction. To investigate this racemisation further, a solution of (*S*)-phenylglycine hydrochloride (**414**) and DBN (**6**) in acetonitrile was stirred at 80 °C. After one hour, the specific rotation of the (*S*)-phenylglycine was found to be +61 ° (*c* = 1.07 g/100 mL in $CHCl_3$), which compares with a literature value of +202 ° (*c* = 0.49 g/100 mL in $CHCl_3$),[215] showing that the acidic stereocentre of the starting material (**414**) is partially racemised under the reaction conditions.

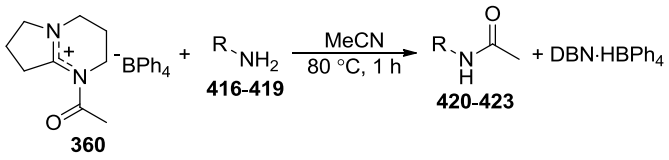


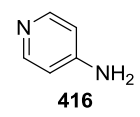
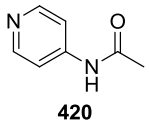
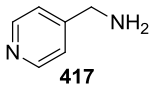
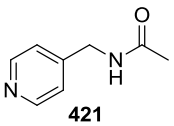
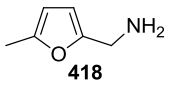
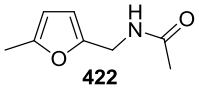
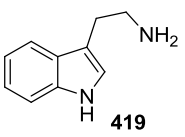
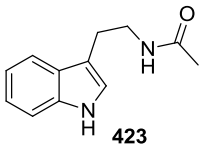
Scheme 92. Acylation of (*S*)-phenylglycine methyl ester hydrochloride (**414**) using *N*-acetyl DBN·BPh$_4$ (**360**) and DBN (**6**) leads to racemisation of the α-stereocentre in the product (**415**).

Next, our *N*-acyl DBN·BPh$_4$ salt acylation methodology was applied to the synthesis of amides containing heteroaromatic fragments, which are often present as structurally important motifs within drug molecules.[150] Firstly, 4-aminopyridine (**416**) was reacted with *N*-acetyl DBN·BPh$_4$ (**360**) in acetonitrile at 80 °C for one hour. Pleasingly, crude ^{1}H NMR analysis showed that the

reaction had proceeded to 96% conversion, enabling *N*-(pyridine-4-yl)acetamide (**420**) to be isolated by washing the crude reaction product with ethyl acetate in 81% yield (Table 10, entry 1). It was reasoned that any pathway leading to pyridine-*N*-acylation products would be reversible, or that they would act as acyl transfer reagents themselves to react with another molecule of 4-aminopyridine (**416**). The reaction of *N*-acetyl DBN·BPh$_4$ (**360**) with 4-picolylamine (**417**) was equally successful, giving *N*-(pyridin-4-ylmethyl)acetamide (**421**) in 78% isolated yield (Table 10, entry 2). 5-Methyl furfurylamine (**418**) was also acylated smoothly under our standard conditions, forming the amide **422** in 97% yield after washing the crude reaction product with ethyl acetate (Table 10, entry 3). However, the reaction of tryptamine (**419**) with *N*-acetyl DBN·BPh$_4$ (**360**) gave 100% conversion but formed a mixture of products (Table 10, entry 4). The desired amide **423** was only isolated in 42% yield, with the product from *N*-acylation of the indole ring observed as the major side product.

Table 10. Acylation of primary amines containing heteroaromatics (**416**-**419**) using *N*-acetyl DBN·BPh$_4$ (**360**).[a]

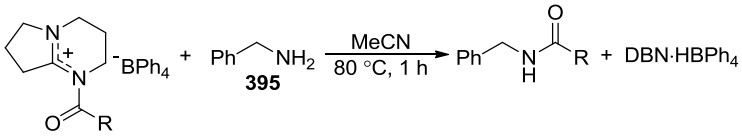


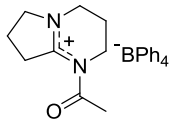
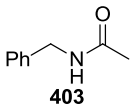
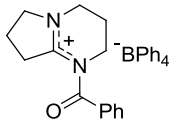
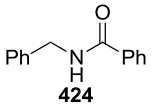
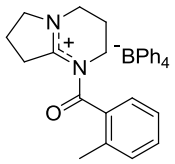
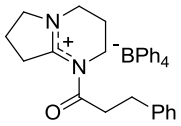
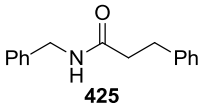
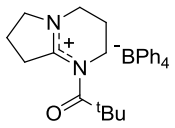
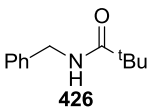
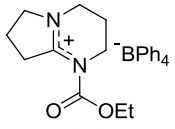
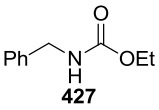
Entry	Amine (**416**-**419**)	Amide (**420**-**423**)	Conversion (%)[b,c]
1	 **416**	 **420**	96 (81)
2	 **417**	 **421**	100 (78)
3	 **418**	 **422**	100 (97)
4	 **419**	 **423**	100 (42)

[a]Reactions performed on a 0.5 mmol scale using 0.65 mmol *N*-acetyl DBN·BPh$_4$ (**360**). [b]Determined by ^{1}H NMR spectroscopic analysis. [c]Isolated yields in parentheses.

Finally, a range of other *N*-acyl DBN·BPh$_4$ salts was investigated for the acylation of benzylamine (**395**). First, benzylamine (**395**) was added to a solution of *N*-benzoyl DBN·BPh$_4$ (**275**) in acetonitrile and heated at 80 °C for one hour. Analysis of the crude ^{1}H NMR spectrum by comparing the integrals of the benzylic proton resonances from the starting material and the

Table 11. Acylation of benzylamine (**395**) using different *N*-acyl DBN·BPh$_4$ salts.[a]



Entry	*N*-acyl DBN·BPh$_4$	Amide	Conversion (%)[b,c]
1	 **360**	 **403**	100 (99)
2[d]	 **275**	 **424**	95 (78)
3	 **361**	-	0 (-)
4	 **362**	 **425**	100 (73)
5	 **363**	 **426**	100 (98)
6	 **364**	 **427**	100 (82)

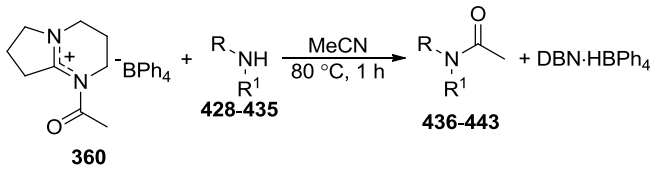
[a]Reactions performed using 0.5 mmol benzylamine (**395**) and 0.65 mmol *N*-acyl DBN·BPh$_4$. [b]Determined by ^{1}H NMR spectroscopic analysis. [c]Isolated yields in parentheses. [d]16 hours reaction time.

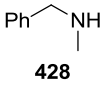
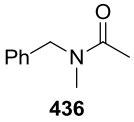
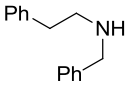
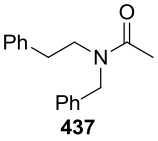
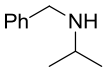
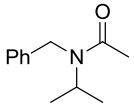
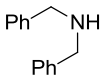
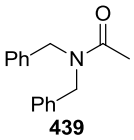
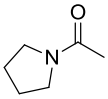
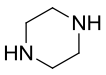
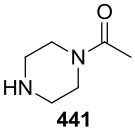
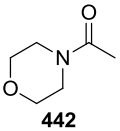
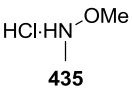
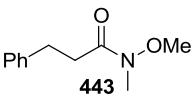
amide (δ = 3.75 ppm and δ = 4.30 ppm respectively) showed that the reaction had only reached 44% conversion. However, increasing the reaction time to 16 hours allowed the benzoylation to reach completion, with *N*-benzyl benzamide (**403**) isolated in 78% yield after the standard work-up procedure (Table 11, entry 2). The acylation of benzylamine (**395**) with bulky *N*-*o*-toluoyl DBN·BPh$_4$ (**361**) was unsuccessful, with no evidence of amide formation by ^{1}H NMR spectroscopy after both one and 16 hours reaction time (Table 11, entry 3). In contrast, reaction with *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**) worked well, giving complete conversion into product within one hour (Table 11, entry 4). The product was isolated by first dissolving the crude reaction product in ethyl acetate and filtering off the insoluble DBN salts before washing the filtrate with 1M HCl, 1M NaOH, and brine, giving pure *N*-benzyl-3-phenylpropanamide (**425**) in 73% yield. The reaction with *N*-pivaloyl DBN·BPh$_4$ (**363**) also worked well, allowing a 98% yield of *N*-benzylpivalamide (**426**) to be obtained using the same work-up procedure as described for the previous example (Table 11, entry 5). The reaction of benzylamine (**395**) with *N*-ethyl carboxyl DBN·BPh$_4$ (**364**) also went to completion within one hour, enabling the corresponding carbamate (**427**) to be isolated in 82 % yield (Table 11, entry 6).

3.2.3.3 *N*-Acylation of Secondary Amines

As *N*-acetyl DBN·BPh$_4$ (**360**) was shown to acylate a wide range of primary amines successfully, this reagent was chosen for the *N*-acylation of secondary amines (Table 12). It was found that the conditions developed for the acylation of primary amines were also applicable to the acylation of secondary amines. For example, *N*-benzyl-*N*-methylamine (**428**) was added to a solution of *N*-acetyl DBN·BPh$_4$ (**360**) in acetonitrile and heated at 80 °C. After one hour the solvent was removed under reduced pressure and the crude reaction product washed with ethyl acetate to remove excess DBN salts to give *N*-benzyl-*N*-methylacetamide (**436**) in 99% yield (Table 12, entry 1). The product (**436**) was analysed using ^{1}H NMR spectroscopy that revealed the presence of a 4:3 mixture of rotamers, with the spectrum showing the characteristic downfield shift of the benzylic protons at δ = 4.50 ppm and δ = 4.44 ppm for the major and minor rotamers respectively. The *N*-acylation protocol also worked well for *N*-benzyl-*N*-phenethylamine (**429**) and gave *N*-benzyl-*N*-phenethylacetamide (**437**) in 98% isolated yield (Table 12, entry 2). The product **437** was analysed by ^{1}H NMR spectroscopy at room temperature as a 1:1 mixture of rotamers. The reaction of *N*-acetyl DBN·BPh$_4$ (**360**) with the more sterically demanding *N*-benzyl-*N*-isopropylamine (**430**) gave a lower 83% conversion into product (**438**) (Table 12, entry 3). The crude product was initially dissolved in ethyl acetate and filtered to remove excess DBN salts and the filtrate was subsequently washed with 1M HCl, 1M NaOH, and brine to remove excess amine (**430**), giving pure *N*-benzyl-*N*-isopropylacetamide

Table 12. Acylation of secondary amines (**428**-**435**) using *N*-acetyl DBN·BPh$_4$ (**360**).[a]



Entry	Amine (**428**-**435**)	Amide (**436**-**443**)	Conversion (%)[b,c]
1	 **428**	 **436**	100 (99)
2	 **429**	 **437**	100 (98)
3	 **430**	 **438**	83 (55)
4[d]	 **431**	 **439**	100 (70)
5[e]	 **432**	 **440**	100 (88)
6[f]	 **433**	 **441**	100 (99)
7	 **434**	 **442**	100 (97)
8[g]	 **435**	 **443**	100 (80)

[a]Reactions performed on a 0.5 mmol scale using 0.65 mmol *N*-acetyl DBN·BPh$_4$ (**360**). [b]Determined by ^{1}H NMR spectroscopic analysis. [c] Isolated yields in parentheses. [d]16 hours. [e]Reaction using 2 equivalents of pyrroldine (**432**). [f]Reaction performed using 0.5 mmol *N*-acetyl DBN·BPh$_4$ (**360**). [g]Reaction performed using 0.65 mmol *N*-hydrocinnamoyl DBN·BPh$_4$ (**362**) and 0.6 mmol DBN (**6**).

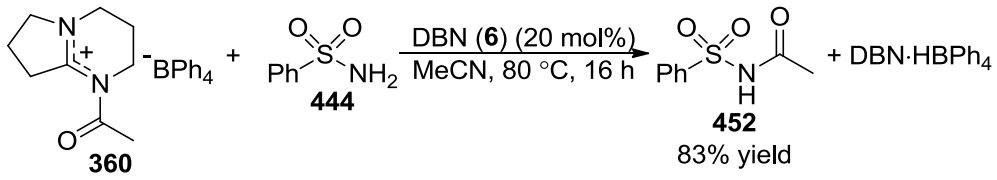
(**438**) in a 55% isolated yield. *N*,*N*-Dibenzylamine (**431**) also reacted slowly, with ^{1}H NMR spectroscopic analysis showing only 38% conversion into the corresponding amide (**439**) in one hour. However, increasing the reaction time to 16 hours gave complete conversion into tertiary amide (**439**) (Table 12, entry 4). The acylation methodology was then applied to cyclic secondary amines. Pyrrolidine (**432**) was reacted with *N*-acetyl DBN·BPh$_4$ (**360**) under the standard conditions for one hour. Although the ^{1}H NMR spectrum of the crude showed 100% conversion, the mass recovery and isolated yield of amide **440** were low. The lower isolated yield was attributed to the volatility of pyrrolidine (**432**), so the reaction was repeated using two equivalents of pyrrolidine (**432**) to one equivalent of *N*-acetyl DBN·BPh$_4$ (**360**) (Table 12, entry 5). In this case the mass recovery was improved, allowing amide **440** to be isolated in 88% yield after filtration using ethyl acetate.

Next, piperazine (**433**) was reacted with one equivalent of *N*-acetyl DBN·BPh$_4$ (**360**) in acetonitrile at 80 °C for one hour (Table 12, entry 6). Analysis of the crude ^{1}H NMR spectrum showed complete conversion into a single amide product (**441**), with no doubly acylated product observed. As expected, morpholine (**434**) worked well as a substrate in the acylation reaction with *N*-acetyl DBN·BPh$_4$ (**360**), giving 1-morpholinoethanone (**442**) in a 97% isolated yield (Table 12, entry 7). Finally, *N*,*O*-dimethylhydroxylamine hydrochloride (**435**) was used as a nucleophile in an attempt to form the corresponding Weinreb amide. *N*-Hydrocinnamoyl DBN·BPh$_4$ (**362**) was used instead of *N*-acetyl DBN·BPh$_4$ (**360**) in order to increase the molecular weight of the Weinreb amide formed. An additional equivalent of DBN (**6**) was also added to the reaction to liberate the nucleophile from its hydrochloride salt (Table 12, entry 8). Pleasingly, analysis of the crude ^{1}H NMR spectrum showed that the reaction had gone to completion in one hour. The Weinreb amide **443** was isolated in 80% yield after removal of the excess DBN·BPh$_4$ salts by filtration from ethyl acetate and subsequent washing of the filtrate with 1M HCl, 1M NaOH, and brine to remove the remaining DBN hydrochloride (**271**).

3.2.4 *N*-Acyl DBN·BPh$_4$ Salts for the *N*-Acylation of Sulfonamides

As *N*-acetyl DBN·BPh$_4$ (**360**) had been shown to be a highly efficient *N*-acylating agent for a wide range of amines it was decided to investigate its use for the acylation of other nucleophiles. *N*-Acyl sulfonamides are important class of compounds in the medicinal and agrochemical industries, with many examples having been reported to exhibit a diverse range of pharmacological activities.[216-218] *N*-Acyl sulfonamides are also widely used as safety-catch linkers in solid support syntheses,[219-220] therefore the use of *N*-acyl DBN·BPh$_4$ salts as acylating agents for sulfonamides was investigated.

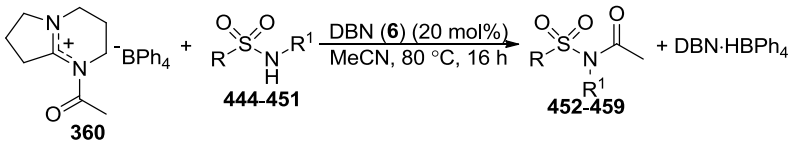
Initially, dry acetonitrile was added to a carousel tube containing *N*-acetyl DBN·BPh$_4$ (**360**) and benzenesulfonamide (**444**) and the resulting solution was heated at 80 °C overnight. Unfortunately, ^{1}H NMR spectroscopic analysis of the crude product showed only 38% conversion into *N*-acetyl benzenesulfonamide (**452**) had been achieved. In an attempt to improve the conversion, a catalytic amount of DBN (**6**) was added to the reaction. It was hoped that the extra DBN (**6**) would initiate the acylation reaction by deprotonating the benzenesulfonamide (**444**) to make a more nucleophilic species that would react more readily with *N*-acetyl DBN·BPh$_4$ (**360**). Pleasingly, the addition of 20 mol% DBN (**6**) was sufficient to allow the reaction of benzenesulfonamide (**444**) with *N*-acetyl DBN·BPh$_4$ (**360**) to proceed to completion (Scheme 93). The crude ^{1}H NMR spectrum showed the characteristic broad resonance at δ = 9.05 ppm for the remaining nitrogen proton and the acetate methyl protons at δ = 2.00 ppm, which was in agreement with data reported in the literature.[221] The reaction was purified by first dissolving the crude reaction product in ethyl acetate and filtering off the insoluble DBN·HBPh$_4$ salt. The filtrate was then washed with NH_4Cl and brine to remove the catalytic amount of DBN (**6**) before being dried and concentrated under reduced pressure to give pure *N*-acetyl benzenesulfonamide (**452**) in an 83% yield.

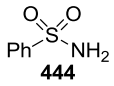
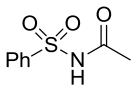
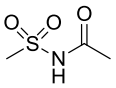
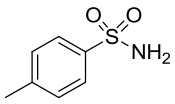
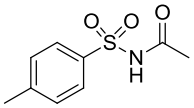
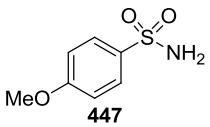
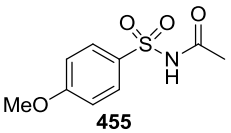
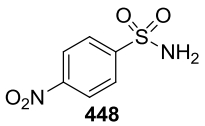
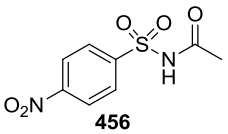
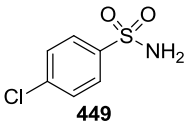
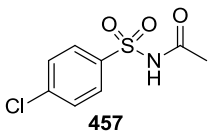
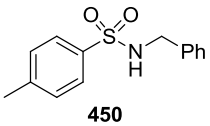
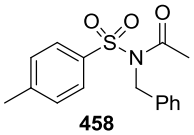
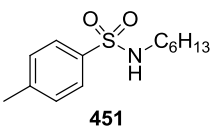
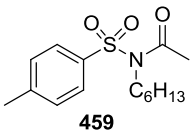


Scheme 93. Acylation of benzenesulfonamide (**444**) using *N*-acetyl DBN·BPh$_4$ (**360**) and 20 mol% DBN (**6**).

The successful acylation conditions using 20 mol% DBN (**6**) were subsequently applied to the acylation of a number of sulfonamides (Table 13). Methanesulfonamide (**445**) was found to be more active than benzenesulfonamide (**444**) when reacted with *N*-acetyl DBN·BPh$_4$ (**360**), giving complete conversion into product (**453**) within 16 hours (Table 13, entry 2). *p*-Toluenesulfonamide (**446**) and *p*-methoxybenzenesulfonamide (**447**) were successfully acylated using *N*-acetyl DBN·BPh$_4$ (**360**) and 20 mol% DBN (**6**) to give the corresponding *N*-acetyl sulfonamides (**454** and **455**) in 92% and 90% conversion in 16 hours (Table 13, entries 3 and 4). The crude reaction mixtures were readily purified by filtration of the excess DBN·BPh$_4$ salts and subsequent extraction of the filtrate to give pure *N*-acetyl sulfonamides **454** and **455** in 80% yield and 74% yield respectively. The reaction of *N*-acetyl DBN·BPh$_4$ (**360**) with less nucleophilic *p*-nitrobenzenesulfonamide (**448**) did not proceed as smoothly, with ^{1}H NMR

Table 13. Acylation of sulfonamides(**444-451**) using *N*-acetyl DBN·BPh$_4$ (**360**).[a]



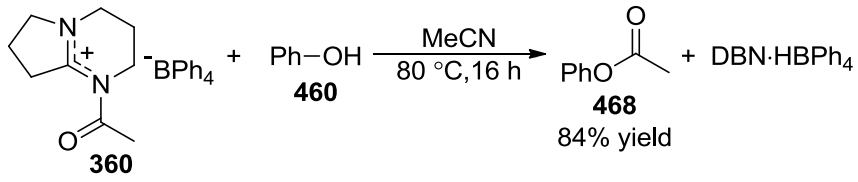
Entry	Sulfonamide (**444-451**)	*N*-Acyl Sulfonamide (**452-459**)	Conversion (%)[b,c]
1	 **444**	 **452**	95 (83)
2	 **445**	 **453**	100 (98)
3	 **446**	 **454**	92 (80)
4	 **447**	 **455**	90 (74)
5	 **448**	 **456**	66 (-)
6	 **449**	 **457**	35 (-)
7	 **450**	 **458**	100 (65)
8	 **451**	 **459**	42 (-)

[a]Reactions performed on a 0.5 mmol scale using 0.65 mmol *N*-acetyl DBN·BPh$_4$ (**360**) and 20 mol% DBN (**6**). [b]Determined by ^{1}H NMR spectroscopic analysis. [c]Isolated yields in parentheses.

spectroscopic analysis of the crude product showing only 66% conversion into *N*-acetyl *p*-nitrobenzenesulfonamide (**456**) (Table 13, entry 5). The acylation of *p*-chlorobenzenesulfonamide (**449**) was even less successful, forming only 35% of the *N*-acylated product (**457**) after 16 hours (Table 13, entry 6). Finally, the methodology was applied to the acylation of two secondary sulfonamides. The acylation of *N*-benzyl *p*-toluenesulfonamide (**450**) with *N*-acetyl DBN·BPh$_4$ (**360**) worked well, giving complete conversion within 16 hours and allowing pure *N*-acetyl *N*-benzyl *p*-toluenesulfonamide (**458**) to be isolated using the standard work-up procedure in 65% yield (Table 13, entry 7). However, the reaction using *N*-hexyl *p*-toluenesulfonamide (**451**) was less successful, with ^{1}H NMR spectroscopic analysis of the crude reaction mixture showing only 42% conversion into product (**459**) with the remaining mass balance comprised of unreacted starting material (Table 13, entry 8).

3.2.5 *N*-Acyl DBN·BPh$_4$ Salts for the *O*-Acylation of Alcohols

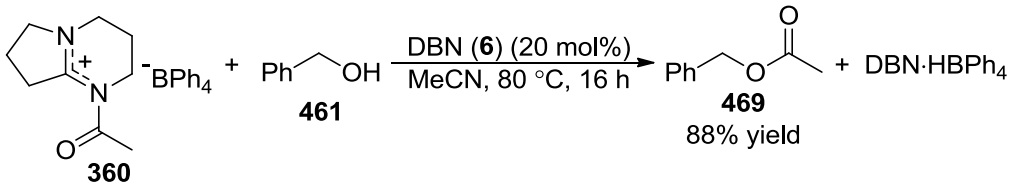
A logical extension of this methodology was to apply the acylation protocol to the formation of esters, another immensely important functional group that is found widely throughout Nature. Phenol (**460**) was the first substrate investigated and was added to a solution of *N*-acetyl DBN·BPh$_4$ (**360**) in acetonitrile and heated at 80 °C for 16 hours. Pleasingly, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed that complete *O*-acylation had occurred. The crude reaction product was dissolved in ethyl acetate and the insoluble DBN·HBPh$_4$ salts removed by filtration. The filtrate was then washed with NH$_4$Cl and brine before being dried and concentrated to give a pure sample of phenyl acetate (**468**) in 84% yield (Scheme 94).



Scheme 94. Acylation of phenol (**460**) using *N*-acetyl DBN·BPh$_4$ (**360**).

The same *O*-acylation procedure was then applied to benzyl alcohol (**461**), however after 16 hours the crude ^{1}H NMR spectrum showed only 36% conversion into benzyl acetate (**469**) with mostly starting material remaining. It was thought that the conversion could be improved by adding a catalytic amount of base to initiate the *O*-acylation in the same way that the *N*-acylation of sulfonamides had been aided by the use of a catalytic amount of DBN (**6**). Therefore, benzyl alcohol (**461**) was added to a solution of *N*-acetyl DBN·BPh$_4$ (**360**) and 20 mol% DBN (**6**) in acetonitrile and heated at 80 °C for 16 hours (Scheme 95). As hoped, the

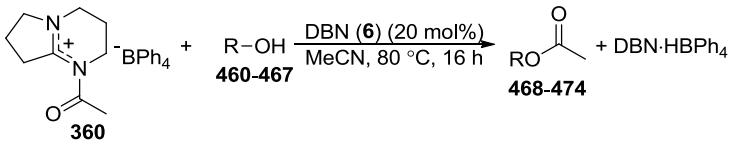
crude ^{1}H NMR spectrum now showed complete conversion into product (**469**) with the characteristic downfield shift of the benzylic protons to δ = 5.03 ppm and no evidence of any starting material. The crude reaction product was purified in the same way as for phenyl acetate (**468**) to give pure benzyl acetate (**469**) in an 88% yield. The fact that phenol (**460**) is more acidic than benzyl alcohol (**461**) makes the proton transfer step more facile, rationalising why additional base was not required in this case.



Scheme 95. Acylation of benzyl alcohol (**461**) using *N*-acetyl DBN·BPh$_4$ (**360**) and 20 mol% DBN (**6**).

The *O*-acylation conditions using 20 mol% DBN (**6**) were then applied to a range of alcohols, the results of which are summarised in Table 14. The reaction of *N*-acetyl DBN·BPh$_4$ (**360**) with phenethyl alcohol (**462**) proceeded as expected, giving phenyl acetate (**470**) in an 80% isolated yield (Table 14, entry 3). The reaction using octanol (**463**) also worked well, with the crude ^{1}H NMR spectrum showing complete conversion into octyl acetate (**471**) within 16 hours (Table 14, entry 4). The *O*-acylation protocol was then applied to a range of secondary alcohols. Pleasingly, 1-phenyl-1-propanol (**464**) was successfully acylated using *N*-acetyl DBN·BPh$_4$ (**360**) and 20 mol% DBN (**6**), forming pure 1-phenylpropyl acetate (**472**) in 79% yield after purification using the standard work-up procedure (Table 14, entry 5). The unsaturated 1-octen-3-ol (**465**) was also acylated under these conditions although, despite the crude ^{1}H NMR spectrum showing complete conversion into product, a reduced 63% isolated yield of oct-1-en-3-yl acetate (**473**) was obtained after work-up (Table 14, entry 6). The cyclic secondary alcohol 1-indanol (**466**) was also shown to react with *N*-acetyl DBN·BPh$_4$ (**360**), giving the corresponding ester (**474**) in 70% isolated yield (Table 14, entry 7). However, reaction with the tertiary alcohol *t*-butanol (**467**) was unsuccessful, with the crude ^{1}H NMR spectrum showing no evidence of any *O*-acylation having occurred (Table 14, entry 8). Attempts to promote the reaction by using an excess of alcohol and then using *t*-butanol (**467**) as the solvent were also unsuccessful, with no *O*-acylation observed in either case.

Table 14. Acylation of alcohols (**460**-**467**) using *N*-acetyl DBN·BPh$_4$ (**360**).[a]

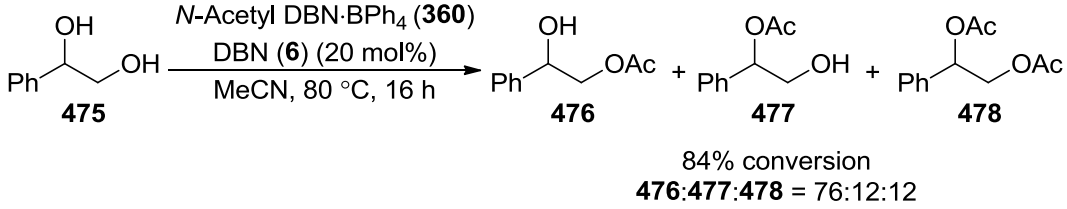


Entry	Alcohol (**460**-**467**)	Ester (**468**-**474**)	Conversion (%)[b,c]
1[d]	Ph−OH **460**	PhO **468**	100 (84)
2	Ph OH **461**	Ph O **469**	100 (88)
3	Ph OH **462**	Ph O **470**	100 (80)
4	$(CH_2)_6$ OH **463**	$(CH_2)_6$ O **471**	100 (74)
5	Et Ph OH **464**	Et Ph O **472**	100 (79)
6	$(CH_2)_4$ OH **465**	$(CH_2)_4$ O **473**	100 (63)
7	OH **466**	O **474**	100 (70)
8	^{t}Bu−OH **467**	-	0 (-)

[a]Reactions performed on a 0.5 mmol scale using 0.65 mmol *N*-acetyl DBN·BPh$_4$ (**360**) and 20 mol% DBN (**6**). [b]Determined by ^{1}H NMR spectroscopic analysis. [c]Isolated yields in parentheses. [d]No DBN (**6**) required.

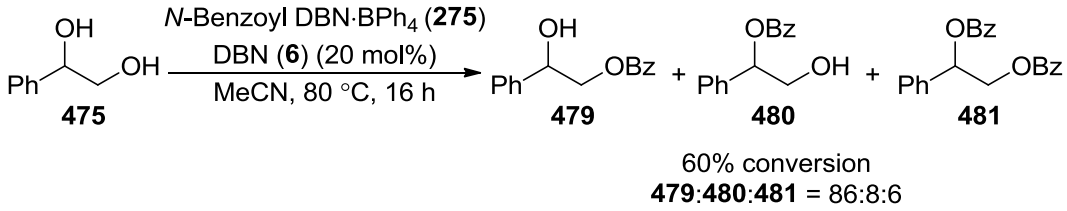
The *O*-acylation protocol using *N*-acetyl DBN·BPh$_4$ (**360**) was then applied to 1-phenyl-1,2-ethanediol (**475**) to investigate whether primary alcohols could be regioselectively acylated in the presence of secondary alcohols (Scheme 96). In this case one equivalent of *N*-acetyl DBN·BPh$_4$ (**360**) was used rather than the 1.3 equivalents used for the previous acylations. The reaction was heated in acetonitrile at 80 °C for 16 hours before excess DBN·HBPh$_4$ salts were removed by filtration. Analysis of the crude ^{1}H NMR spectrum showed four distinct doublets of

doublets at δ = 4.7, 4.9, 5.8, and 6.0 ppm corresponding to unreacted diol (**475**), the primary acylated product (**476**), the secondary acylated product (**477**), and the di-acylated product (**478**) respectively. Analysis of the integrals of the four signals showed that the reaction had proceeded to 84% conversion, with 76% of the converted material was the primary acylated ester (**476**). However, the reaction was not completely regioselective as 12% of the secondary ester (**477**) and 12% of the di-acylated ester (**478**) were also formed.



Scheme 96. Regioselective *O*-acylation of 1-phenyl-1,2-ethanediol (**475**) with *N*-acetyl DBN·BPh$_4$ (**360**).

The regioselectivity for primary over secondary alcohol acylation was further improved by using *N*-benzoyl DBN·BPh$_4$ (**275**) instead of *N*-acetyl DBN·BPh$_4$ (**360**). The crude ^{1}H NMR spectrum showed that the primary ester (**479**), the secondary ester (**480**), and the di-acylated product (**481**) were formed in an 86:8:6 ratio, although the overall conversion was lowered to 60% (Scheme 97).



Scheme 97. Regioselective *O*-acylation of 1-phenyl-1,2-ethanediol (**475**) with *N*-benzoyl DBN·BPh$_4$ (**275**).

3.3 Conclusions

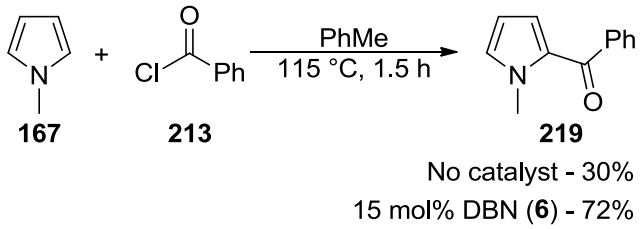
In conclusion, *N*-acyl DBN·BPh$_4$ salts have been demonstrated to be versatile reagents for a number of acylation reactions. A broad range of bench-stable, crystalline *N*-acyl DBN·BPh$_4$ salts have been synthesised, which are easier to handle than their corresponding acyl chlorides as they do not react with moisture in air to form HCl gas. The utility of these *N*-acyl DBN·BPh$_4$ salts for reaction with a range of nucleophiles has been investigated. Pleasingly, the salts were shown to be highly efficient *N*-acylating agents for a number of primary and secondary amines, allowing the amide products to be isolated in pure form *via* a simple work-up procedure without the need for column chromatography. *N*-Acetyl DBN·BPh$_4$ (**360**) was shown to react with

primary and secondary sulfonamides in the presence of a catalytic amount of DBN (**6**). Finally, the *N*-acyl DBN·BPh_4 salts were used for the *O*-acylation of primary and secondary alcohols, with ester products isolated without the need for column chromatography.

4 Iodide as a Nucleophilic Catalyst

4.1 Introduction

The DBN (**6**) catalysed Friedel-Crafts acylation reaction of pyrroles and indoles described in Chapter 2 represents the first organocatalytic version of this reaction. However, under the reaction conditions employed there is still an appreciable background rate and the DBN (**6**) gives a rate enhancement of approximately 2.5 times (Scheme 98), whilst the reaction is cleaner and higher isolated yields are obtained when using the catalyst.[222]



Scheme 98. The rate of Friedel-Crafts acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) is enhanced by approximately 2.5 times using DBN (**6**) as a catalyst.

Having optimised and probed the mechanism of the DBN (**6**) catalysed reaction it was decided to return to the original problem of finding an efficient catalyst for the Friedel-Crafts acylation of heteroaromatics that gives a significant rate enhancement. Preliminary experiments showed that lithium bromide and lithium iodide might be suitably active nucleophilic catalysts for the acylation of pyrroles with acyl chlorides.

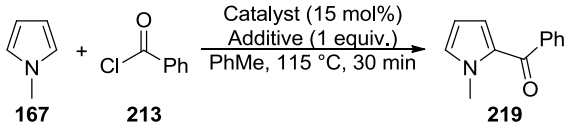
4.2 Results and Discussion

Whilst attempting to improve the rate enhancement given by DBN (**6**) on the Friedel-Crafts acylation of *N*-methylpyrrole (**167**) it was found that adding an equivalent of lithium bromide significantly improved the rate of the reaction (Table 15). The uncatalysed reaction between *N*-methylpyrrole (**167**) and benzoyl chloride (**213**) in toluene heated at 115 °C for 30 minutes showed only 7% conversion into acyl pyrrole (**219**) by ^{1}H NMR spectroscopic analysis of the crude reaction product using 2,5-dimethylfuran as an internal standard (Table 15, entry 1). The addition of 15 mol% DBN (**6**) did not significantly improve the rate of reaction, forming only 12% of *C*2-acyl pyrrole (**219**) after 30 minutes (Table 15, entry 2).[**] However, the reaction

[**] The conversion is lower than for the optimised DBN (**6**) catalysed Friedel-Crafts acylation in Chapter 2 (page 41) as these reactions were performed at a lower concentration and for a shorter reaction time.

using 15 mol% DBN (**6**) and one equivalent of LiBr showed complete conversion into a single regioisomer by ^{1}H NMR spectroscopy, with the characteristic *C*2-acyl pyrrole proton resonances at δ = 6.92, 6.74, and 6.16 ppm integrating quantitatively with those for the 2,5-dimethylfuran standard at δ = 5.85 ppm (Table 15, entry 3). The use of one equivalent of LiBr without any DBN (**6**) also improved the conversion into 44% but is still much less than when both were used together, suggesting a synergistic effect between the DBN (**6**) and the LiBr (Table 15, entry 4).

Table 15. Effect of additives on the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**).[a]



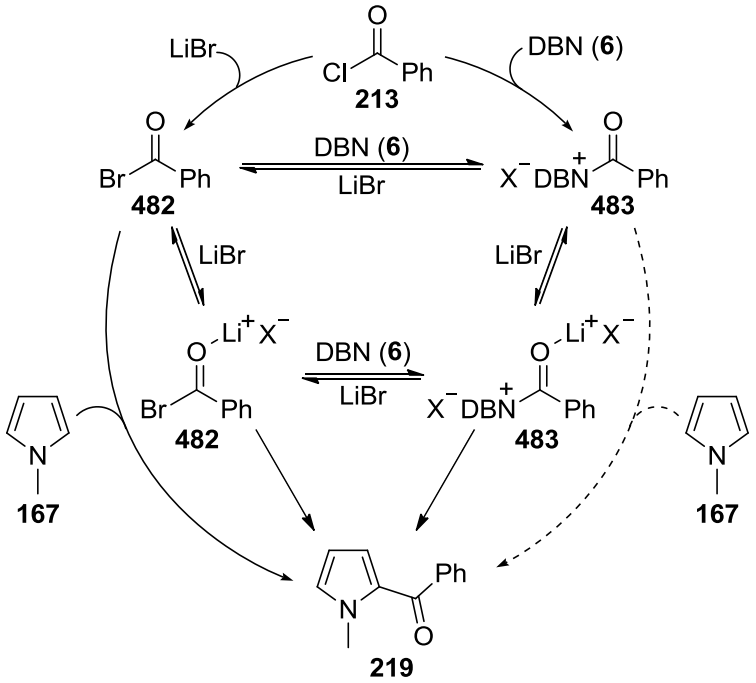
167 **213** **219**

Entry	Catalysts	Additive	Conversion (%)[b]
1	-	-	7
2	DBN (6)	-	12
3	DBN (6)	LiBr	100
4	-	LiBr	44

[a]Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**213**) in 0.5 mL PhMe. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard.

There are a number of possible routes by which DBN (**6**) and LiBr could promote the Friedel-Crafts acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**), with the main possibilities summarised in Scheme 99. The LiBr could act as either a Lewis acid and/or a nucleophilic catalyst during the process. As LiBr without any DBN (**6**) gives 44% conversion into product there must be a significant pathway in which DBN (**6**) is not involved. One possibility is that the LiBr acts as a Lewis acid towards the acyl chloride (**213**), making it more electrophilic. Alternatively, the bromide ion could displace the chloride to make an acyl bromide (**482**), which would be more reactive than the acyl chloride (**213**). The acyl bromide (**482**) could be further activated by a second molecule of LiBr acting as a Lewis acid. However, when DBN (**6**) and LiBr were used together the conversion was increased to 100% within 30 minutes, suggesting that DBN (**6**) also plays a significant role in the reaction. It is known from the previous studies (Chapter 2, page 52) that DBN (**6**) can nucleophically activate the acyl chloride (**213**) to form an *N*-acyl DBN intermediate (**483**). However, as DBN (**6**) on its own only gives 12% conversion into product, the direct reaction of the *N*-acyl DBN **483** with *N*-

methylpyrrole (**167**) must only be a minor reaction pathway. Therefore, the role of the *N*-acyl DBN **483** could be to facilitate the formation of the acyl bromide (**482**), otherwise the LiBr might simply be acting as a Lewis acid towards the *N*-acyl DBN **483** to increase its reactivity.

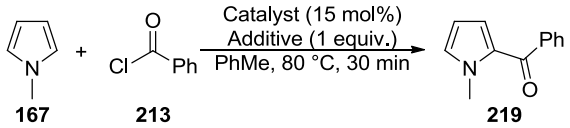


Scheme 99. Potential roles of DBN (**6**) and LiBr in the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**).

The effect of the nature of the additive used in the reaction was further investigated to both gain an insight into the mechanism of the reaction and further improve reactivity to allow milder conditions to be used for the acylation reaction. Therefore, the reaction temperature was reduced to 80 °C and a range of lithium salts was screened as additives for the acylation of *N*-methylpyrrole (**167**) and benzoyl chloride (**213**) (Table 16). Under these reaction conditions, the uncatalysed reaction and the reaction with DBN (**6**) without any additive resulted in no product formation by analysis of the crude ^{1}H NMR spectra after 30 minutes (Table 16, entries 1 and 2). The addition of one equivalent of LiCl did not promote the reaction (Table 16, entry 3), but reaction using LiBr did show 13% conversion into *C*2-acyl pyrrole (**219**) (Table 16, entry 4). The use of LiI as an additive showed the biggest improvement, with ^{1}H NMR spectroscopic analysis of the crude reaction mixture showing 56% conversion into a single regioisomer of product (Table 16, entry 5). These results suggest that the salt anion was key to the catalytic activity and that Lewis acid catalysis by the lithium ion was not responsible for the increase in reactivity. This is supported by the fact that the bulky non-nucleophilic perchlorate anion is unreactive, despite the fact that it is a good source of lithium for Lewis acid catalysis (Table 16,

entry 6).[223] The results also show the expected trend in reactivity if the reaction proceeds *via* the corresponding acyl halide intermediate ($I^- > Br^- > Cl^-$).

Table 16. Effect of additives on the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**).[a]

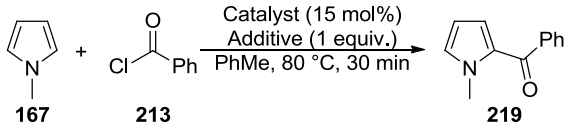


Entry	Catalysts	Additive	Conversion (%)[b]
1	-	-	<1
2	DBN (**6**)	-	<1
3	DBN (**6**)	LiCl	<1
4	DBN (**6**)	LiBr	13
5	DBN (**6**)	LiI	56
6	DBN (**6**)	$LiClO_4$	<1

[a]Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**213**) in 0.5 mL PhMe. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard.

As LiI had been shown to be the most effective additive under the milder reaction conditions further experiments were performed to assess the synergistic nature of using both DBN (**6**) and LiI (Table 17). *N*-Methylpyrrole (**167**) and benzoyl chloride (**213**) were reacted in toluene at 80 °C with combinations of DBN (**6**) and LiI and the reaction time was increased to one hour. As seen previously, the uncatalysed reaction and the reaction using solely DBN (**6**) did not form any acylated product (Table 17, entries 1 and 2). However, the reaction using 15 mol% DBN (**6**) and one equivalent of LiI gave 54% conversion by ^{1}H NMR spectroscopic analysis of the crude (Table 17, entry 3). Surprisingly, the reaction with LiI without any DBN (**6**) proceeded to an even higher 64% conversion after one hour (Table 17, entry 4), showing that there was no synergistic effect between DBN (**6**) and LiI under these reaction conditions.

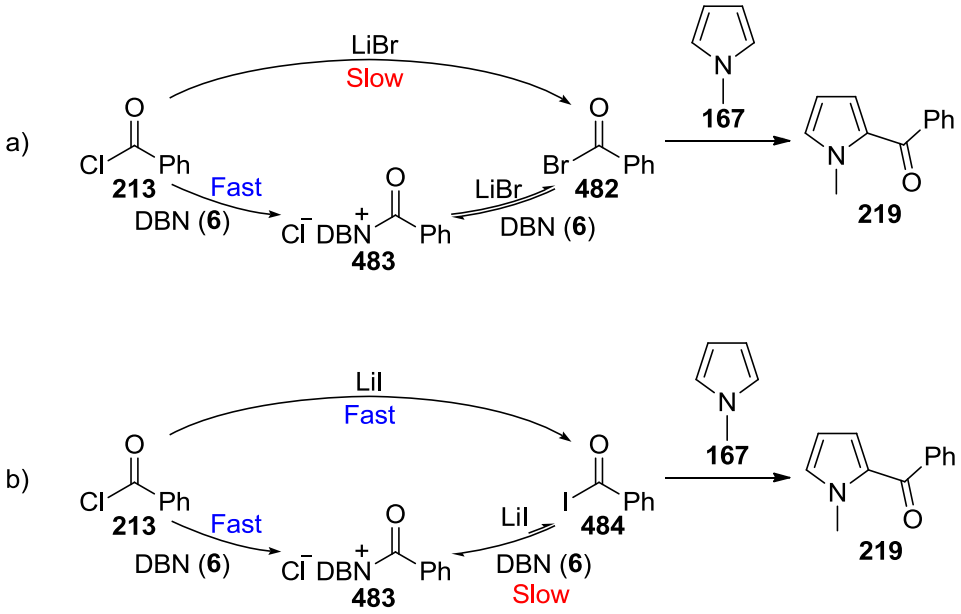
Table 17. Effect of DBN (**6**) and LiI on the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**).[a]



Entry	Catalysts	Additive	Conversion (%)[b]
1	-	-	<1
2	DBN (**6**)	-	<1
3	DBN (**6**)	LiI	54
4	-	LiI	64

[a]Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**213**) in 0.5 mL PhMe. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard.

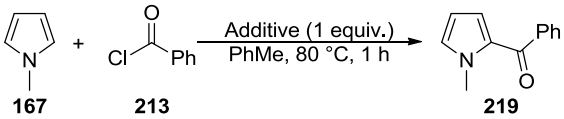
The fact that no synergistic effect was observed using LiI and DBN (**6**) for the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**), but there is cooperation between LiBr and DBN (**6**) can potentially be rationalised by considering the nucleophilicity and steric bulk of the iodide and bromide anions (Scheme 100). As the reaction of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) using lithium salts follows the trend expected if it proceeds *via* the corresponding acyl iodide (**484**), the formation of the acyl iodide (**484**) intermediate is key to explaining the differences in the reactivity. As bromide is less nucleophilic than iodide, the formation of the acyl bromide (**482**) by direct reaction of LiBr with the acyl chloride (**213**) is slower than the formation of the acyl iodide (**484**) using LiI. However, in the presence of DBN (**6**) an activated *N*-acyl DBN intermediate **483** is formed, which is known to be more reactive than the acyl chloride (**213**). Therefore, the smaller bromide anion may attack the *N*-acyl DBN **483** to form the acyl bromide (**482**), increasing the overall rate of acyl bromide (**482**) formation. However, the bulkier iodide anion, although more nucleophilic, may not be able to attack the *N*-acyl DBN intermediate (**483**) as easily and as a consequence the presence of the DBN (**6**) with LiI actually slows down the reaction as the *N*-acyl DBN **483** remains unreacted.



Scheme 100. Difference in reactivity of a) LiBr and b) LiI in the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**).

As the previous reactions had suggested that iodide was catalysing the Friedel-Crafts acylation of *N*-methylpyrrole (**167**), sources of iodide other than LiI were investigated (Table 18). However, using one equivalent of both NaI and KI in the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) gave lower conversions into *C*2-acyl pyrrole (**219**) (54% and 13% respectively) compared with the 62% observed with LiI (Table 18, entries 1-3). The use of *tert*-butyl ammonium iodide as an additive was unsuccessful, with no conversion into product

Table 18. Screen of iodide salts for the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**).[a]



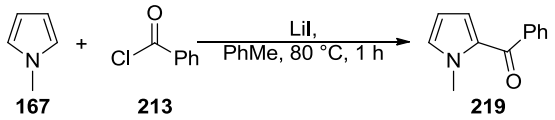
Entry	Additive	Conversion (%)[b]
1	LiI	62
2	NaI	54
3	KI	13
4	Bu_4NI	<1

[a]Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**213**) in 0.5 mL PhMe. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard.

observed by ^{1}H NMR spectroscopic analysis of the crude after one hour (Table 18, entry 4). These results are consistent with the idea that iodide is acting as a nucleophilic catalyst to form the acyl iodide. The salts give increasing conversion into product with increasing ionic nature (LiI > NaI > KI) and therefore increasing availability of the iodide anion.[224]

The amount of LiI used in the acylation reactions was then screened to see if a catalytic amount of iodide could be used (Table 19). The standard reaction using *N*-methylpyrrole (**167**) and benzoyl chloride (**213**) in toluene at 80 °C was performed using varying amounts of LiI. It was found that conversion into acylated product decreased with decreasing amounts of LiI (Table 19, entries 1-5). Unfortunately, the results show that the iodide is not efficient in sub-stoichiometric quantities as only limited catalytic turnover is observed. Increasing the amount of LiI beyond one equivalent did not increase conversion into product further (Table 19, entry 6). However, as LiI is an inexpensive and relatively available reagent it is feasible to use it in a stoichiometric amount to promote the reaction.

Table 19. Equivalents of LiI for the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**).[a]



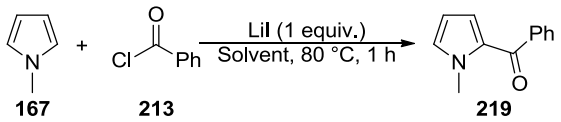
Entry	Equivalents of LiI	Conversion (%)[b]
1	0	0
2	0.1	16
3	0.2	34
4	0.5	48
5	1	60
6	1.5	56

[a]Reactions performed on a 1 mmol scale using 1.2 mmol benzoyl chloride (**213**) in 0.5 mL PhMe. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard.

The acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) using one equivalent of LiI as a catalyst was then further optimised. It was found that using an excess of *N*-methylpyrrole (**167**) instead of excess benzoyl chloride (**213**) was more effective and that the reaction could be diluted by a factor of two without significantly reducing conversion. The results of a solvent

screen for the reaction of *N*-methylpyrrole (**167**) and benzoyl chloride (**213**) using one equivalent of LiI at 80 °C for one hour are summarised in Table 20. The use of less polar solvents such as hexane and 1,4-dioxane gave reasonable conversions into product (**219**) (45% and 58% respectively) but were not significant improvements on the use of toluene (43% conversion) (Table 20, entries 1-3). The reaction using THF as a solvent was completely inhibited, with the crude ^{1}H NMR spectrum only showing 7% conversion into acylated product (**219**) (Table 20, entry 4). This provides further evidence that iodide is acting as a nucleophilic catalyst, as acyl iodides have been reported to ring-open cyclic ethers such as THF.[225-226] The reaction in ethyl acetate was more successful, with a single regioisomer of acylate pyrrole (**219**) observed in 80% conversion after one hour (Table 20, entry 5). The use of more polar solvents such as 1,2-DCE and acetonitrile gave improved conversion compared with toluene (63% and 77% respectively), but were not as high as for reaction in ethyl acetate (Table 20, entries 6 and 7). Further analysis of the crude ^{1}H NMR spectrum of the reaction in ethyl acetate showed the presence of benzoic acid through the presence of a distinctive doublet at δ = 8.15 ppm, whilst the crude ^{13}C{^{1}H} NMR spectrum showed a small carbonyl peak at δ = 172 ppm also corresponding to the acid.

Table 20. Solvent screen for the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) and LiI.[a]



167 **213** **219**

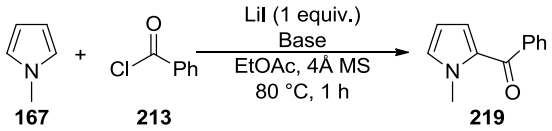
Entry	Solvent	Conversion (%)[b]
1	Hexane	45
2	PhMe	43
3	1,4-Dioxane	58
4	THF	7
5	EtOAc	80
6	1,2-DCE	63
7	MeCN	77
8	EtOAc + 4Å MS	97
9[c]	EtOAc + 4Å MS	0%

[a]Reactions performed on a 1 mmol scale using 1.3 mmol of *N*-methylpyrrole (**167**) in 1 mL of solvent. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c]No LiI.

Comparing the integrals of the resonances due to the acid with those of the 2,5-dimethylfuran internal standard showed that approximately 10% benzoic acid was present in the crude reaction mixture. This is likely to have been formed by hydrolysis of either benzoyl chloride (**213**) or the proposed benzoyl iodide (**484**) intermediate by water present in the ethyl acetate. Pleasingly, repeating the reaction in ethyl acetate using 4Å molecular sieves increased the conversion into *C*2-acyl pyrrole (**219**) to 97%, with no trace of benzoic acid in the crude ^{1}H NMR spectrum (Table 20, entry 8). It is thought that the sole role of the molecular sieves is to remove any water, preventing unwanted side reactions. There is no reaction between *N*-methylpyrrole (**167**) and benzoyl chloride (**213**) in ethyl acetate with 4Å molecular sieves in the absence of LiI (Table 20, entry 9).

Whilst conditions had been found to form *C*2-benzoyl pyrrole (**219**) in almost quantitative conversion without decomposition, there was a concern about the generation of HI during the reaction. Unlike the DBN (**6**) catalysed reaction that was performed in toluene at 115 °C where the HCl formed was released from the reaction mixture (Chapter 2, page 55), the HI or HCl generated in this process are likely to be more soluble in the ethyl acetate and remain in solution. This could lead to problems with acid-catalysed polymerisation of more sensitive and reactive *C*2-acyl pyrroles. Therefore a range of organic and inorganic bases was screened in the

Table 21. Effect of base on the acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) and LiI.[a]



Entry	Base	Conversion (%)[b]
1	-	97
2	Et_3N	18
3	2,6-Lutidene	57
4	DBU	0%
5	Cs_2CO_3	83%
6	K_2CO_3	58%

[a]Reactions performed on a 1 mmol scale using 1.3 mmol of *N*-methylpyrrole (**167**) in 1 mL EtOAc with 4Å MS. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c]No LiI.

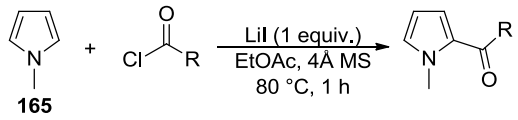
reaction to neutralise any HI (or HCl) formed (Table 21). However, adding an equivalent of an organic base such as triethylamine, 2,6-lutidine, or DBU (**5**) significantly decreased the rate of reaction between *N*-methylpyrrole (**167**) and benzoyl chloride (**213**) using LiI (Table 21, entries 1-4). This was not entirely unexpected as it was known from previous work that bases such as these can also act as nucleophiles. For example, DBU (**5**) is very nucleophilic and would readily react with the acyl chloride (or any acyl iodide formed) to give an *N*-acyl DBU intermediate that was known to be unreactive under these reaction conditions. The more sterically hindered and therefore least nucleophilic base 2,6-lutidine gave the best result with 57% conversion into product (Table 21, entry 2), but this was much less than the corresponding reaction without base (Table 21, entry 1). The use of one equivalent of an inorganic base such as caesium or potassium carbonate was more successful, giving 83% and 58% conversion respectively (Table 21, entries 5 and 6), but this is still significantly lower than the reaction without base.

It was concluded that the optimal conditions for the lithium iodide catalysed acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) do not require the presence of a base to remove any HI or HCl that is generated. Consequently, it was reasoned that employing a short reaction time of one hour and using a milder temperature (80 °C) would help prevent acid-catalysed polymerisation of more sensitive *C*2-acyl pyrroles.

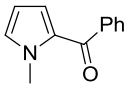
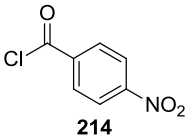
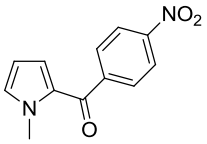
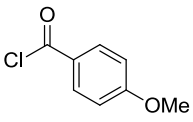
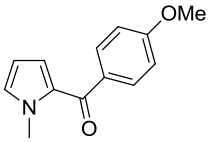
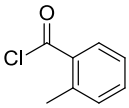
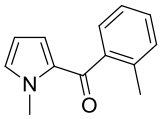
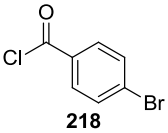
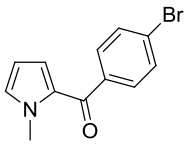
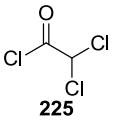
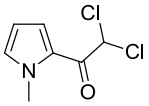
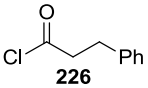
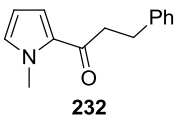
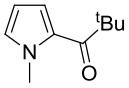
4.2.1 Acyl Chloride Substrate Scope

The scope of the acyl chloride fragment was then investigated using various acyl chlorides with *N*-methylpyrrole (**167**) and one equivalent of LiI in ethyl acetate with 4Å molecular sieves at 80 °C for one hour (Table 22). The excess lithium salts were removed *via* filtration before the crude reaction mixture was concentrated and analysed by ^{1}H NMR spectroscopy using an internal standard of 2,5-dimethylfuran. Pleasingly, the protocol worked for both electron-withdrawing *p*-nitrobenzoyl chloride (**215**) and electron-donating *p*-methoxybenzoyl chloride (**215**), with complete conversion into the corresponding *C*2-acyl pyrroles within one hour (Table 22, entries 2 and 3). However, the acylation was slower using the more sterically demanding *o*-toluoyl chloride (**216**), requiring four hours to reach 76% conversion (Table 22, entry 4). The reaction was then shown to work well for *p*-bromobenzoyl chloride (**218**), forming the *C*2-acyl product (**224**) regioselectively with 100% conversion (Table 22, entry 5). Next, the protocol was applied to the acylation of *N*-methylpyrrole (**167**) with non-aromatic acyl chlorides. The reaction with dichloroacetyl chloride (**225**) proceeded smoothly, giving complete conversion into the *C*2-acylated pyrrole (**231**) in one hour (Table 22, entry 6), whilst reaction with hydrocinnamoyl chloride (**226**) required four hours to reach completion (Table 22, entry 7). The

Table 22. Acylation of *N*-methylpyrrole (**167**) with a range of acyl chlorides.[a]



165

Entry	Acyl chloride	Acyl pyrrole	Conversion (%)[b]
1	 **213**	 **219**	97
2	 **214**	 **220**	100
3	 **215**	 **221**	100
4[c]	 **216**	 **222**	76
5	 **218**	 **224**	100
6	 **225**	 **231**	100
7[c]	 **226**	 **232**	100
8[d]	 **230**	 **235**	50

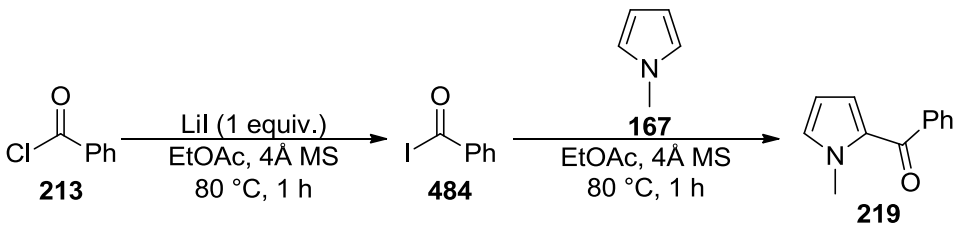
[a]Reactions performed on a 1 mmol scale using 1.3 mmol of *N*-methylpyrrole (**167**) in 1 mL EtOAc with 4Å MS. [b]Determined by ^{1}H NMR spectroscopic analysis using 2,5-dimethylfuran as an internal standard. [c] 4 h reaction time. [d]20 h reaction time.

acylation of *N*-methylpyrrole (**167**) with sterically demanding pivaloyl chloride (**230**) only proceeded to 15% conversion after one hour under the standard conditions. Increasing the reaction time to 20 hours only improved the conversion to 50% (Table 22, entry 8), which suggests that the *C*2-acylated product (**235**) and/or *N*-methylpyrrole (**167**) are decomposed when subjected to the acidic reaction conditions for extended periods of time.

4.2.2 Mechanism of the Lithium Iodide Catalysed Friedel-Crafts Acylation of Pyrrole

The evidence from optimisation of the lithium iodide catalysed Friedel-Crafts acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) suggests that the iodide acts as a nucleophilic catalyst to form an intermediate acyl iodide (**484**), which is significantly more reactive than the parent benzoyl chloride (**213**). The possibility that lithium acts as a Lewis acid to activate the carbonyl was ruled out on the basis that using different sources of lithium (LiCl, LiBr, and $LiClO_4$) decreases the rate of reaction (Table 18). Whilst LiI is more ionic than these other sources of lithium and would therefore be expected to be a better Lewis acid,[224] the coordinating solvent ethyl acetate was found to be optimal for the reaction. Therefore the lithium is most likely to act as a Lewis acid towards the excess of ethyl acetate present in the reaction mixture. The coordination of the lithium to the ethyl acetate would also make the iodide ion more available, possibly explaining why this proved to be the best solvent for the reaction. Other sources of iodide, such as NaI, KI, and Bu_4NI, do not promote the acylation as efficiently as LiI, presumably due to the decreased availability of the iodide ion in these salts compared with the more ionic LiI.

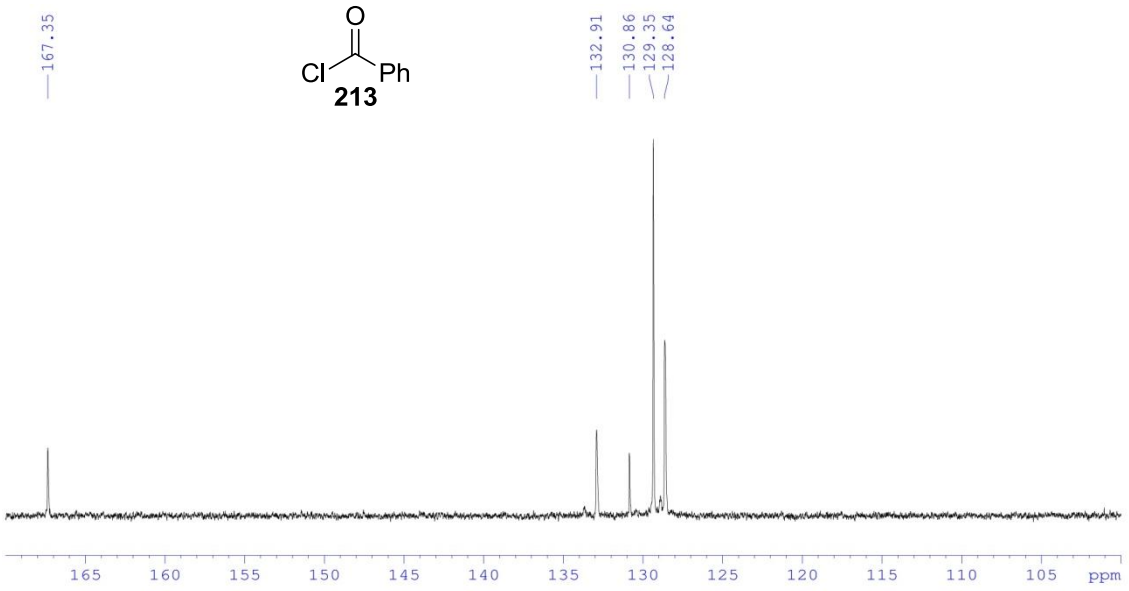
Further proof for a benzoyl iodide (**484**) intermediate came from the reaction of one equivalent of LiI with benzoyl chloride (**213**) under the optimised reaction conditions (Scheme 101). After one hour an aliquot of the reaction mixture was taken and analysed by ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopy.



Scheme 101. Formation of the acyl iodide (**484**) intermediate from benzoyl chloride (**213**) and LiI followed by reaction with *N*-methylpyrrole (**167**) to form the *C*2-acyl pyrrole (**219**).

The ^{1}H NMR spectrum of the reaction mixture showed distinct differences in the aromatic region compared with the spectrum of benzoyl chloride (**213**). The $^{13}C\{^{1}H\}$ NMR spectrum provided the clearest evidence of the formation of benzoyl iodide (**484**), showing a strong carbonyl signal at δ = 159.7 ppm and no resonance at δ = 167.4 ppm due to the benzoyl chloride (Figure 12a and b), with other chemical shifts consistent with those previously reported for benzoyl iodide (**484**).[227] The upfield chemical shift of the carbonyl resonance of benzoyl iodide (**484**) is due to the heavy-atom effect of iodine, with an increase in diamagnetic shielding caused by the extra electrons introduced by the iodine atom.[227-228]

a) ^{1}H NMR, 300 MHz, DMSO-d_6



b) ^{1}H NMR, 300 MHz, DMSO-d_6

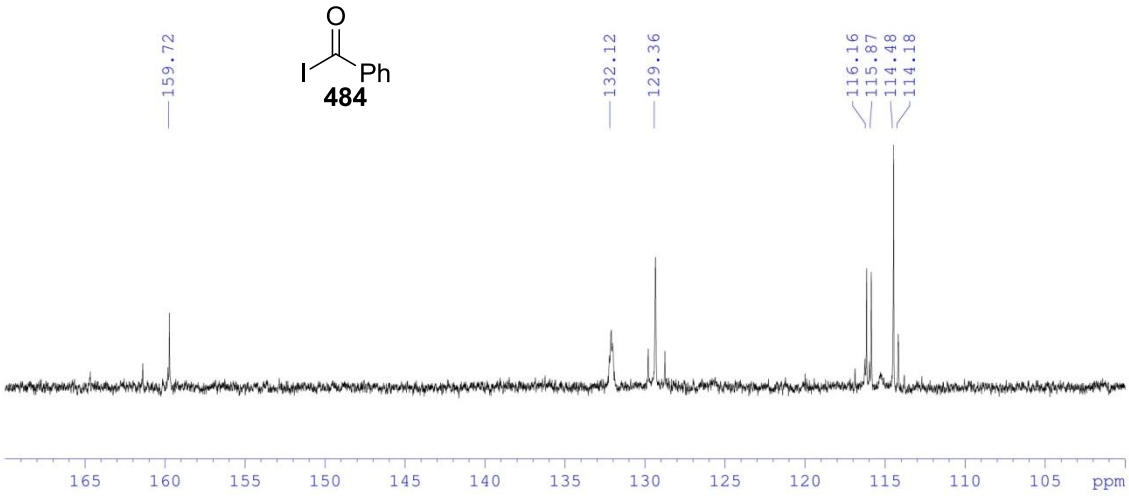


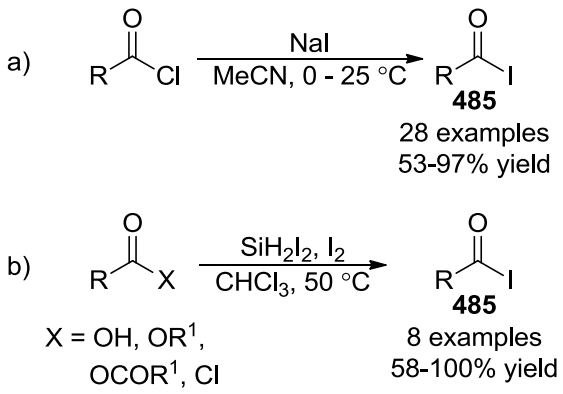
Figure 12. 300 MHz ^{1}H NMR spectra of a) benzoyl chloride (**213**) and b) benzoyl iodide (**484**) formed from the reaction of benzoyl chloride (**213**) with LiI in ethyl acetate.

The remainder of this reaction mixture was then transferred into a second carousel tube that contained fresh 4Å molecular sieves using a filter cannula to remove excess LiCl that had precipitated out of solution. *N*-Methylpyrrole (**167**) was then added and the solution heated to 80 °C for a further hour, after which time the solution was concentrated and analysed. The crude ^{1}H NMR spectrum showed that the *C*2-acyl pyrrole (**219**) has been form quantitatively by comparison of the integrals of pyrrolic protons with the signals from the 2,5-dimethylfuran internal standard, proving that the benzoyl iodide (**484**) readily acylates *N*-methylpyrrole (**167**) under the reaction conditions.

4.2.3 Acyl Iodides in Organic Synthesis

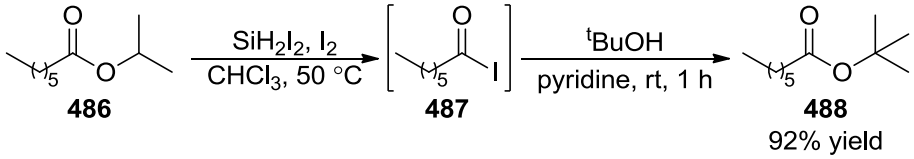
Acyl iodides are considerably more reactive acylating agents than their corresponding acyl chlorides or acyl bromides. The increased reactivity of acyl iodides can be rationalised by the decreased dissociation of the C-I bond compared with other acyl halides. For example, the C-I bond dissociation energy of acetyl iodide is 192.5 KJmol^{-1}, whereas the bond dissociation energies of acetyl fluoride, chloride, and bromide are 460, 321, and 260 KJmol^{-1} respectively.[229-230] The decreased bond dissociation energy of acyl iodides can in turn be rationalised by the increased size of the iodine atom compared with the other halides, which decreases overlap of n_{Hal} with the π^* anti-bonding orbital of the carbonyl.

However, despite their increased reactivity compared with other acyl halides, there are a limited number of methods of preparing acyl iodides and only a few reports of their use in organic synthesis. Benzoyl iodide (**484**) was first synthesises in 1832 by Liebig and Wohler by reacting benzoyl chloride with potassium iodide.[231] In 1981, Hoffmann and Haase developed the most common method of synthesising acyl iodides (**485**) by reacting acyl chlorides with sodium iodide in acetonitrile using reactor-extractor apparatus (Scheme 102a).[227] Keinan and Sahai reported a useful alternative to this procedure using diiodosilane and iodine, which allowed the synthesis of acyl iodides (**485**) from carboxylic acids, esters, lactones, anhydrides, and acyl chlorides (Scheme 102b).[231]



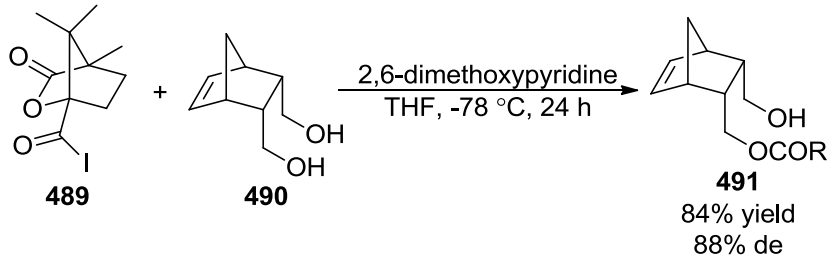
Scheme 102. Synthesis of acyl iodides (**485**) using a) sodium iodide and b) diiodosilane.[227,231]

Keinan and Sahai demonstrated the synthetic utility of their methodology by synthesising a *tert*-butyl ester (**488**) from heptanoyl iodide (**487**), which was prepared from isopropyl heptanoate (**486**) using diiodosilane and iodine (Scheme 103).[231]



Scheme 103. Synthesis of a *tert*-butyl ester (**488**) using heptanoyl iodide (**487**).[231]

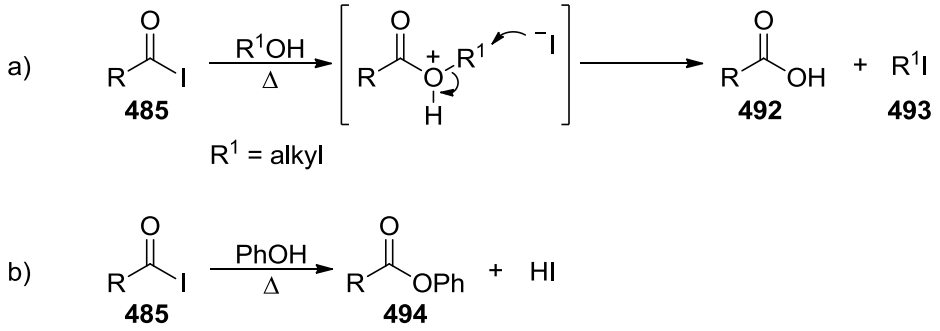
Yamamoto and co-workers have used the sterically bulky (1*S*,4*R*)-(-)-camphanoyl iodide (**489**) as a stereoselective acylating agent for a range of *meso*-diols. For example, *meso*-diol **490** is acylated efficiently using acyl iodide **489** at low temperature to give the corresponding mono-ester (**491**) in high yield with good diastereoselectivity (Scheme 104).[232]



Scheme 104. Stereoselective acylation of *meso*-diol **490** using (1*S*,4*R*)-(-)-camphanoyl iodide (**489**).[232]

Since 2002, Voronkov and co-workers have published over twenty papers on the reaction of simple acyl iodides, namely acetyl and benzoyl iodide, with a range of functional groups (Scheme 106). The majority of the reactions reported are performed by heating the acyl iodide

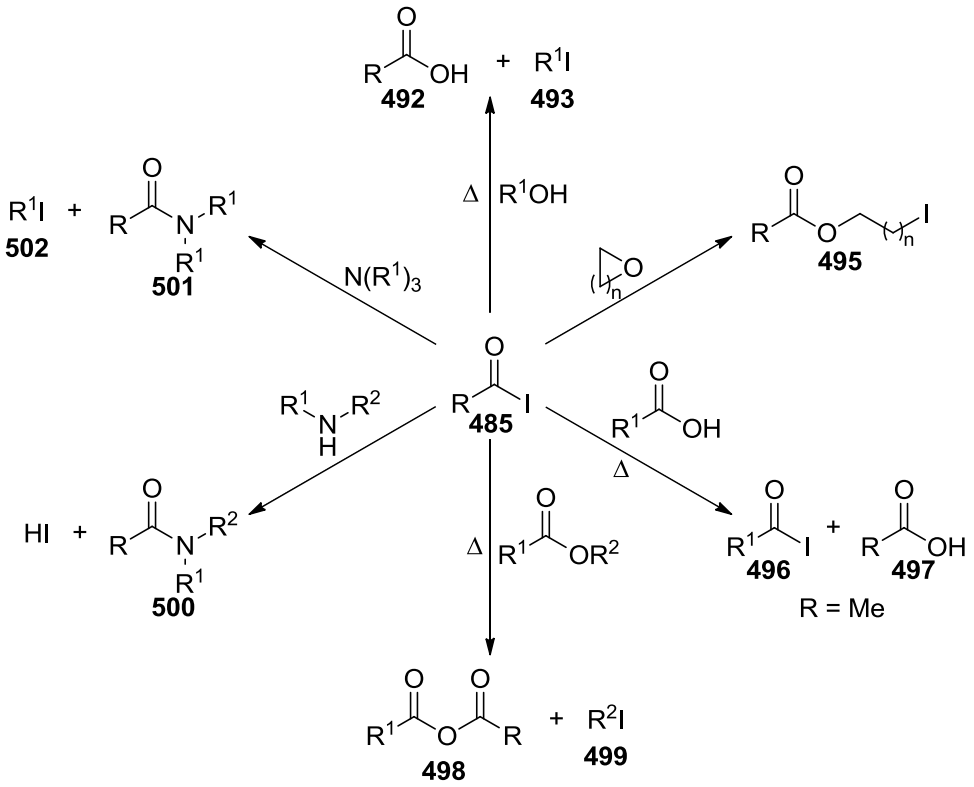
and the substrate neat, whilst those reactions that do not require external heating are highly exothermic. These relatively harsh reaction conditions gave rise to unexpected products in some cases. For example, heating alkyl alcohols with acetyl or benzoyl iodide forms the corresponding carboxylic acid (**492**) and the alkyl iodide (**493**) instead of the expected ester. It is proposed that the alcohol initially reacts with the acyl iodide (**485**) to form a protonated ester, before the liberated iodide undergoes an S_N2 reaction with this intermediate to form a carboxylic acid (**492**) and an alkyl iodide (**493**) (Scheme 105a). However, reaction of both acetyl and benzoyl iodide with phenol did afford the expected phenolate ester (**494**) due to the increased acidity of phenol compared with alkyl alcohols and its inability to undergo an S_N2 reaction (Scheme 105b).[233]



Scheme 105. The reaction of acyl iodides (**485**) with a) alkyl alcohols and b) phenol.[233]

The reactions of acyl iodides (**485**) with other common functional groups reported by Voronkov and co-workers are summarised in Scheme 106. It was shown that acyl iodides (**485**) react exothermically with both acyclic and cyclic ethers, resulting in *O*-acylation and concomitant C-O bond cleavage with iodide to form iodo-esters (**495**).[225] This is consistent with the observations of Amouroux *et al*.[226] and Nozaki *et al*.[234] who found that acyl iodides (**485**) can be used to regioselectively ring-open 2-methyltetrahydrofuran and propylene oxide respectively. The reaction of acyl iodides (**485**) with cyclic ethers may explain why THF was found to be a poor solvent for the Friedel-Crafts acylation reaction (Table 20, entry 4). The reaction of aliphatic acyl chlorides with carboxylic acids usually forms the corresponding anhydride and releases HCl, however heating carboxylic acids with acetyl iodide (**485**, R = Me) results in an exchange process to form a new acyl iodide (**496**) and acetic acid (**497**).[230] Voronkov and co-workers found that acyl iodides (**485**) react with esters to form an anhydride (**498**) and an alkyl iodide (**499**), presumably through attack of the ester carbonyl on the acyl iodide (**485**) followed by S_N2 attack of the iodide anion on the resulting intermediate.[235] It was shown that acyl iodides (**485**) undergo *N*-acylation reactions with both primary and secondary amines, forming the corresponding amides (**500**) without any external heating.[236-238] However, the reaction of acyl

iodides (**485**) with tertiary amines results in unusual C-N bond cleavage, forming a secondary amide (**501**) and an alkyl iodide (**502**).[239]

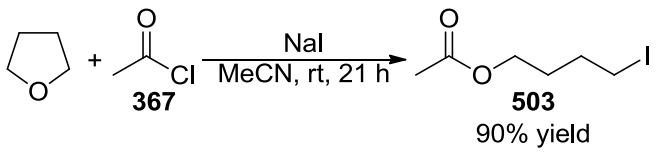


Scheme 106. Summary of some of the reactions of acyl iodides (**485**) reported by Voronkov and co-workers.[233-239]

4.2.4 *In Situ* Formation of Acyl Iodides

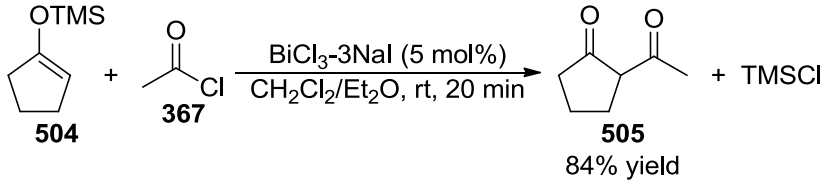
Despite the widespread use of the Finkelstein reaction, forming alkyl iodides from the equilibrium exchange of alkyl chlorides and bromides with sodium iodide in acetone,[151] to increase the reactivity of the alkyl halides, there are comparatively few reports of the *in situ* generation of acyl iodides from acyl chlorides.

In 1909, Kishner first reported that benzoyl chloride (**213**) and potassium iodide could be used to cleave diethyl ether. Oku *et al*. subsequently showed that acetyl iodide (**485**, R = Me), generated *in situ* from acetyl chloride (**367**) and NaI, could be used to ring-open THF to form the iodo-ester **503** in 90% yield (Scheme 107).[240] This efficient methodology has subsequently been used by Sloan and Thomas to synthesise iodo-esters from trioxane[241] and has also recently been used by Bates and Dewey in the total synthesis of swainsonine, a potent mannosidase inhibitor.[242]



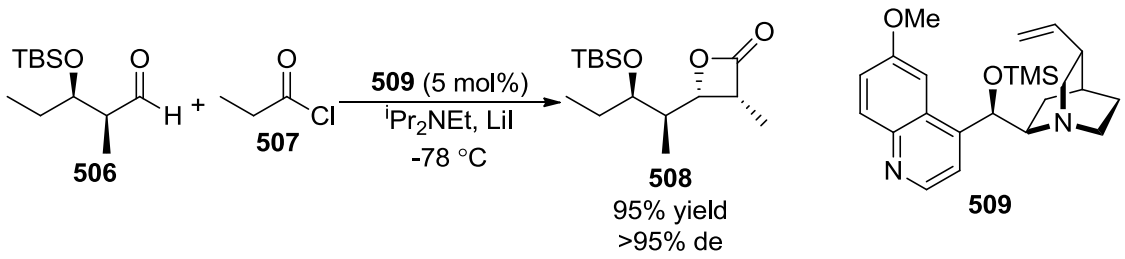
Scheme 107. Ring-opening of THF using acetyl iodide generated *in situ* from acetyl chloride (**367**) and NaI.[240]

Dubac *et al*. suggested that an acyl iodide intermediate might be formed in the *C*-acylation of silyl enol ethers (**504**) using acetyl chloride (**367**) and 5 mol% $BiCl_3$-3NaI as a catalyst (Scheme 108). However, Dubac *et al*. have not reported any detailed mechanistic investigations, with the nature of any interaction between the $BiCl_3$ and the acetyl chloride (**367**) (or acetyl iodide) currently unknown.[243]



Scheme 108. *C*-acylation of 1-(trimethylsiloxy)cyclopentene (**504**) with acetyl chloride (**367**) in the presence of $BiCl_3$ and NaI.[243]

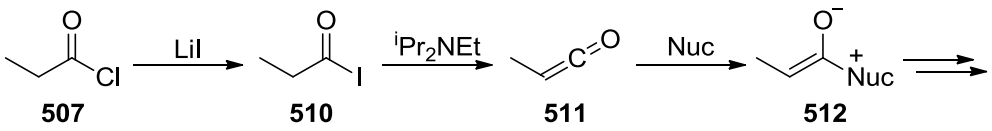
There are also examples in the literature of reactions involving acyl chlorides that use LiI and NaI as additives where the role of the salt is not stated, or unknown. For example, Nelson *et al*. have used LiI as an additive in a cinchona alkaloid (**509**) catalysed ketene-aldehyde cycloaddition reaction for the formal synthesis of erythromycin B (Scheme 109).[244]



Scheme 109. LiI as an additive in a cinchona alkaloid (**509**) catalysed ketene-aldehyde cycloaddition.[244]

The role of the LiI in this reaction was not stated by Nelson *et al*., but the reaction is known to proceed *via* a ketene intermediate. Therefore, a potential role of the LiI might be to convert the acyl chloride (**507**) to the acyl iodide (**510**), whose α-protons would be more acidic than the acyl chloride α-protons and thus the ketene (**511**) would be more easily formed (Scheme 110). The ketene (**511**) could then react with the cinchona alkaloid (**509**) nucleophilic catalyst before

undergoing an enantioselective addition to the aldehyde (**506**). This contrasts with the original report on this methodology, where Nelson *et al*. used $LiClO_4$ as an additive and speculated that it acted as a Lewis acid towards the activated ketene (**512**), allowing formation of a six-membered transition state with the incoming aldehyde.[245]

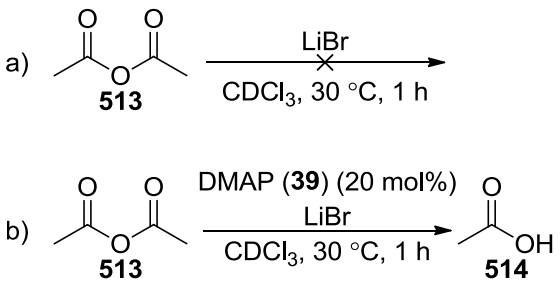


Scheme 110. Possible role of LiI in the ketene-aldehyde cycloaddition.

4.2.5 Activation of Anhydrides using Lithium Salts

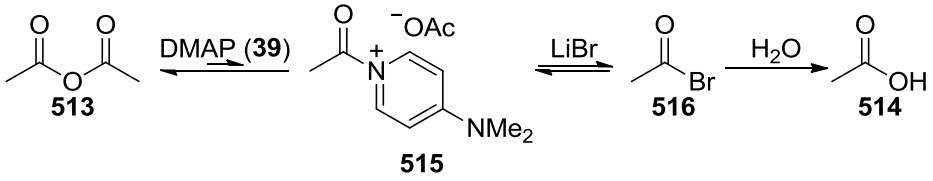
Metallic iodides such as LiI and NaI have also been used to hydrolyse esters[246-247] and NaI has been used in a one-pot benzyl ether deprotection and subsequent acetylation sequence using acetic anhydride.[248] The exact role of the LiI or NaI in these processes has never been determined experimentally, although in the case of ester hydrolysis Karlsson proposed that the lithium acts as a Lewis acid and coordinates to the ester carbonyl.[246] However, there is the possibility that these processes also proceed *via* an acyl iodide intermediate and, as a consequence, the reaction of lithium salts with acetic anhydride were studied.

An attempt was made to observed any potential acyl halide intermediate in the reactions of acetic anhydride (**513**) using $^{13}C\{^{1}H\}$ NMR spectroscopic analysis. Firstly, one equivalent of LiBr and acetic anhydride (**513**) were stirred in $CDCl_3$ at 30 °C for one hour (Scheme 111a). The reaction mixture was filtered and analysed by $^{13}C\{^{1}H\}$ NMR spectroscopy, which showed that no reaction had taken place and only the peaks due to acetic acid at δ = 166 and 22 ppm were present. The reaction was then repeated in the presence of 20 mol% DMAP (**39**), with the crude $^{13}C\{^{1}H\}$ NMR spectrum showing mostly unreacted acetic anhydride (**513**) but, importantly, also showing a small peak at δ = 175 ppm, which corresponds to the carbonyl peak of acetic acid (**514**) (Scheme 111b).



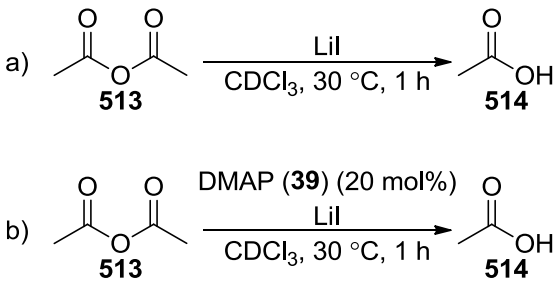
Scheme 111. The reaction of acetic anhydride (**513**) with a) LiBr and b) LiBr and 20 mol% DMAP (**39**).

The presence of acetic acid (**514**) in the $^{13}C\{^{1}H\}$ NMR spectrum shows that LiBr and DMAP promote the hydrolysis of acetic anhydride (**513**), presumably by water present in the $CDCl_3$ solvent. One of the potential mechanisms for this hydrolysis is shown in Scheme 112. The fact that reaction with just LiBr and acetic anhydride (**513**) without DMAP (**39**) does not form any acetic acid (**514**) suggests that the bromide anion cannot directly add to acetic anhydride (**513**) to form the acyl bromide. However, it has been shown that a solution of acetic anhydride (**513**) and DMAP (**39**) exists as an equilibrium with *N*-acetyl DMAP (**515**), although free acetic anhydride (**513**) predominates.[146] The bromide anion could potentially add to the *N*-acetyl DMAP (**515**) to form acetyl bromide (**516**), which would be readily hydrolysed by any adventitious water to form acetic acid (**514**). However, as acetyl bromide (**516**) was not observed directly in the crude $^{13}C\{^{1}H\}$ NMR spectrum the LiBr could potentially be acting as a Lewis acid to promote the addition of DMAP (**39**) to acetic anhydride (**513**) to form an activated *N*-acetyl DMAP (**515**), which could then be hydrolysed directly.



Scheme 112. Possible activation of acetic anhydride (**513**) using DMAP (**39**) and LiBr.

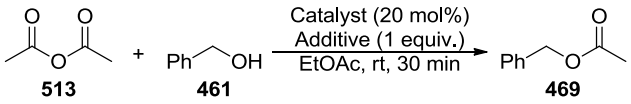
The above reactions were then repeated using LiI instead of LiBr (Scheme 113). In both cases the crude $^{13}C\{^{1}H\}$ NMR spectrum showed the formation of acetic acid (**514**) to a greater extent than observed with LiBr and DMAP (**39**) (Scheme 111b). The fact that LiI promotes the hydrolysis of acetic anhydride (**513**) in the absence of DMAP (**39**) whereas LiBr is inactive is intriguing. This could be due to the fact that iodide is more nucleophilic than bromide and can therefore add to acetic anhydride (**513**) to form acetyl iodide (**485**, R = Me), which is subsequently hydrolysed. Alternatively, it could be that LiI is more dissociated than LiBr and therefore a stronger Lewis acid that can activate acetic anhydride (**513**) towards direct hydrolysis. However, as the $^{13}C\{^{1}H\}$ NMR spectrum of both reactions showed no evidence of acetyl iodide it is difficult to distinguish between the two possibilities.



Scheme 113. The reaction of acetic anhydride (**513**) with a) LiI and b) LiI and 20 mol% DMAP (**39**).

This activation was further studied by investigating the potential of LiI to act as an acylation catalyst using acetic anhydride (**513**) and benzyl alcohol (**461**) (Table 23). It was found that one equivalent of LiI gives 48% conversion into benzyl acetate (**469**) in 30 minutes (Table 23, entry 2), whereas no conversion is observed when no additive is used (Table 23, entry 1). However, the use of 20 mol% DMAP (**39**) as a catalyst resulted in complete conversion into product (Table 23, entry 3). Interestingly, using both DMAP (**39**) and LiI gave comparable conversion with that observed using only LiI (Table 23, entry 4).

Table 23. Acylation of acetic anhydride (**513**) with benzyl alcohol (**461**) using LiI.[a]



Entry	Catalyst	Additive	Conversion (%)[b]
1	-		0
2	-	LiI	48
3	DMAP (**39**)	-	100
4	DMAP (**39**)	LiI	50

[a]Reactions performed on a 1 mmol scale in 1 mL EtOAc. [b]Determined by ^{1}H NMR spectroscopic analysis.

Despite the fact that no direct evidence for the formation of acyl halides from acetic anhydride has been observed, these experiments suggest that lithium salts may prove to be useful catalysts for acylation reactions using acetic anhydride (**513**).

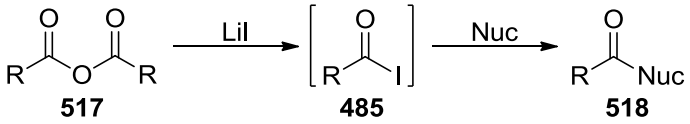
4.3 Conclusions

The potential of iodide to act as a nucleophilic catalyst has been demonstrated. It was found that the rate of Friedel-Crafts acylation of *N*-methylpyrrole (**167**) with benzoyl chloride (**213**) was

significantly increased using LiBr as an additive. Extensive optimisation of the process showed that using one equivalent of LiI in ethyl acetate at 80 °C gave complete conversion into the *C*2-acytlated product within one-hour, with no background rate observed under these conditions. The LiI is thought to act as a source of iodide, which acts as a nucleophilic catalyst towards the acyl chloride. Evidence of an acyl iodide intermediate in the reaction has been obtained through ^{1}H and $^{13}C\{^{1}H\}$ NMR spectroscopic analysis of the reaction mixture. Preliminary experiments also suggest that acid anhydrides may also be nucleophically activated using LiI, which would significantly increase the scope of this methodology.

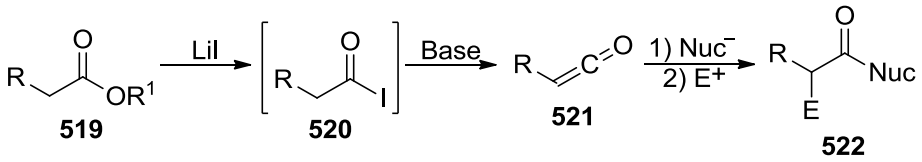
4.4 Further Work

If the activation of anhydrides using LiI is shown to proceed *via* an acyl iodide intermediate, using iodide as a nucleophilic catalyst, then there are a number of potential uses of this methodology in organic synthesis. The simplest use of LiI activation of anhydrides would be for the acylation of nucleophiles, with literature precedent for *C*-, *N*-, and *O*-acylations using acyl iodides (**485**) (Scheme 114).



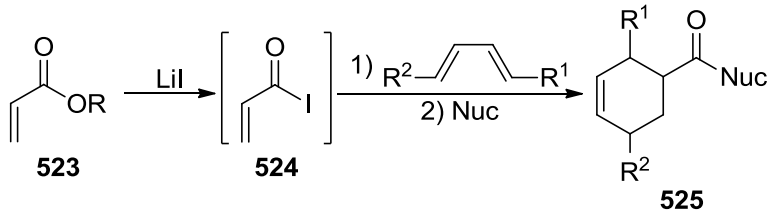
Scheme 114. The activation of anhydrides (**517**) with LiI to promote acylation of nucleophiles.

If the LiI activation could be extended further to use esters as substrates, potentially using a second nucleophilic catalyst such as DMAP (**39**) to aid formation of the acyl iodide, then the acylation methodology would offer a significant advantage to methods currently available. Acyl iodide intermediates (**520**) generated *in situ* from esters (**519**) could also be useful as precursors to ketenes (**521**), as suggested for the ketene-aldehyde cycloaddition reported by Nelson *et al.* (Scheme 109). The ketene (**521**) generated could then react with a nucleophile to form an enolate that could be quenched with an electrophile to form α-functionalised carbonyl compounds (**522**) (Scheme 115).



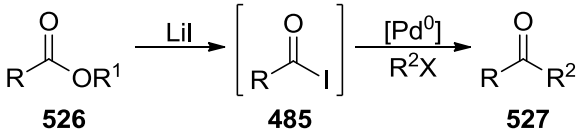
Scheme 115. The use of LiI to activate esters towards ketene formation (**522**).

α,β-Unsaturated acyl iodides (**524**) should be more electron deficient than the corresponding α,β-unsaturated ester (**523**) and therefore should react faster with dienes in Diels-Alder reactions (Scheme 116). This nucleophilic activation of esters using iodide would provide a Lewis acid free method of catalysing Diels-Alder reactions and the residual LiI could be readily removed from the crude reaction mixture through an aqueous wash.



Scheme 116. Nucleophilic activation of α,β-unsaturated esters (**523**) with iodide to catalyse the Diels-Alder reaction.

Finally, combining the nucleophilic activation of esters with iodide with transition metal catalysis would be a significant area of interest. For example, a palladium based catalyst should readily undergo insertion into the C-I bond of an acyl iodide (**485**) allowing cross-coupling reactions to occur (Scheme 117). Overall, this would provide a method of forming ketones (**527**) from esters (**526**) using a combination of nucleophilic and transition metal catalysis.



Scheme 117. Combining nucleophilic activation of esters (**526**) with iodide and palladium catalysed cross-coupling.

5 Experimental

5.1 General Experimental

All reactions were performed under a nitrogen atmosphere in oven-dried apparatus, unless otherwise stated. Anhydrous acetonitrile, dichloromethane, tetrahydrofuran, and toluene were obtained from an Innovative Technology Inc. PS-400-7 solvent purification system. Petrol refers to the fraction of petroleum ether boiling at 40-60 °C. Pyrrole (**236**) and *N*-methylpyrrole (**167**) were distilled before use. All other commercially available compounds were used as obtained from the chemical suppliers. Analytical thin layer chromatography was performed using commercially available aluminium backed plates coated with Merck G/UV254 neutral silica. Plates were visualised under UV light (at 254 nm) or by staining with phosphomolybdic acid followed by heating. Flash chromatography was performed using chromatography grade, silica 60 Å particle size 35-70 microns from Fisher Scientific.

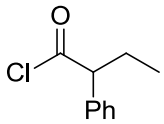
^{1}H NMR spectra were recorded at either 500 MHz or 300 MHz and ^{13}C{^{1}H} spectra were recorded at either 125 MHz or 75 MHz on a Brüker Avance 500 or Brüker Avance 300 spectrometer respectively. Chemical shifts, δ, are quoted in parts per million and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; m, multiplet; app., apparent and br., broad. Coupling constants, *J*, are quoted to the nearest 0.1 Hz. High resolution mass spectra were recorded on a Brüker Daltonics microTOF spectrometer with an electrospray source and external calibration. Masses were recorded in positive electrospray ionisation mode and were introduced by flow injection. Masses are accurate to 5 ppm and data was processed using DataAnalysis software from Brüker Daltonics. Infra red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with selected absorbances quoted as ν in cm^{-1}. Optical rotations were recorded on an Optical Activity Ltd AA-10 automatic polarimeter with a path length of 1 dm; concentrations (c) are quoted in g/100 mL. All capillary melting points were measured using Stuart digital SMP10 melting point apparatus with 1 degree resolution.

X-ray data were collected at 150 K on a Nonius KappaCCD area detector diffractometer using Mo-Kα radiation (λ = 0.71073 Å). All structures were solved by direct methods and refined on all *F2* data using SHELXL-97 suite of programs, with hydrogen atoms included in idealized positions and refined using the riding model.

5.2 Organocatalytic Friedel-Crafts Acylation of Pyrroles and Indoles

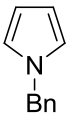
5.2.1 Starting Material Compound Data

2-Phenylbutanoyl chloride (229)[249]



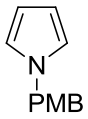
2-Phenylbutyric acid (1.64 g, 10 mmol) was dissolved in dichloromethane (3 mL) in a nitrogen purged round-bottomed flask. DMF (0.04 mL, 0.5 mmol) and thionyl chloride (0.87 mL, 12 mmol) were added and the resulting solution was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure before being re-dissolved in 1:1 hexane : Et_2O. The solution was extracted with H_2O before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the title compound (1.42 g, 78%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.34-7.18 (5H, m, Ph*H*), 3.81 (1H, t, *J* = 7.5 Hz, C*H*Ph), 2.22-2.08 (1H, m, C*H*^{A}H^{B}CH$_3$), 1.87-1.72 (1H, m, CH^A*H*^{B}CH$_3$), 0.86 (3H, t, *J* = 7.4 Hz, C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 175.10, 136.03, 129.19, 128.54, 128.38, 65.33, 26.75, 11.87; IR (film, cm^{-1}): ν_{max} = 1794 (C=O), 1495, 1454.

1-Benzyl-1*H*-pyrrole (237)[137]



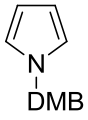
Based on a literature procedure,[137] sodium hydride (60% dispersion in mineral oil, 1.32 g, 33 mmol) was added to anhydrous DMF (30 mL) in a nitrogen purged two-neck round-bottom flask. The solution was cooled to 0 °C and pyrrole (**236**) (2.08 mL, 30 mmol) in anhydrous DMF (8 mL) was added dropwise. The solution was allowed to warm to room temperature and was stirred for 30 minutes before being cooled back to 0 °C when benzyl bromide (3.57 mL, 30 mmol) was added dropwise. The solution was again allowed to warm to room temperature and was stirred for one hour. The solution was then added to H_2O and extracted with 1:1 hexane : Et_2O. The combined organic layers were washed with H_2O before drying over $MgSO_4$, filtering, and concentrating under reduced pressure. The crude product was purified by flash column chromatography (hexane : Et_2O (95:5), R_f = 0.64), yielding the title compound (3.60 g, 76%) as a yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.39-7.27 (3H, m, Ar*H*), 7.18-7.11 (2H, m, Ar*H*), 6.72 (2H, app. t, *J* = 1.6 Hz, C*H*N), 6.22 (2H, app. t, *J* = 1.6 Hz, C*H*CHN), 5.09 (2H, s, NC*H*$_2$Ph); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 138.3, 128.8, 127.8, 127.1, 121.3, 108.6, 53.5.

1-(4-Methoxybenzyl)-1*H*-pyrrole (238)[138]



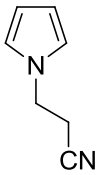
Based on a literature procedure,[138] 2,5-dimethoxytetrahydrofuran (**250**) (1.30 mL, 10 mmol), 4-methoxybenzylamine (1.30 mL, 10 mmol), and glacial acetic acid (5 mL) were added to a carousel tube and heated at 115 °C for 1.5 hours. The reaction was allowed to cool before being diluted with EtOAc and quenched with $NaHCO_3$. The resulting layers were separated and the organics washed with brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petrol : EtOAc (95:5), R_f = 0.44), yielding the title compound (0.98 g, 52%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.08 (2H, d, *J* = 8.5 Hz, Ar*H*), 6.86 (2H, d, *J* = 8.6 Hz, Ar*H*), 6.68 (2H, t, *J* = 1.9 Hz, C*H*N), 6.18 (2H, t, *J* = 1.9 Hz, C*H*CHN), 5.01 (2H, s, NCH_2), 3.80 (3H, s, OCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 159.3, 130.3, 128.6, 121.1, 114.2, 108.5, 55.4, 53.0.

1-(2,4-Dimethoxybenzyl)-1*H*-pyrrole (239)



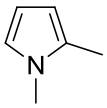
Based on a literature procedure,[138] 2,5-dimethoxytetrahydrofuran (**250**) (0.26 mL, 2 mmol), 2,4-dimethoxybenzylamine (0.30 mL, 2 mmol), and glacial acetic acid (2 mL) were added to a carousel tube and heated at 115 °C for 1.5 hours. The reaction was allowed to cool before being diluted with EtOAc and quenched with $NaHCO_3$. The resulting layers were separated and the organics washed with brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petrol : EtOAc (95:5), R_f = 0.38), yielding the title compound (0.21 g, 49%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 6.81 (1H, d, *J* = 8.2 Hz, Ar*H*), 6.71 (2H, t, *J* = 2.0 Hz, C*H*N), 6.46 (1H, d, *J* = 2.4 Hz, Ar*H*), 6.41 (1H, dd, *J* = 8.3, 2.4 Hz, Ar*H*), 6.15 (2H, t, *J* = 2.0 Hz, C*H*CHN), 5.00 (2H, s, NCH_2), 3.83 (3H, s, OCH_3), 3.79 (3H, s, OCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 160.7, 157.9, 129.5, 121.2, 119.3, 108.0, 104.2, 98.6, 55.6, 55.5, 48.0; IR (film, cm^{-1}): ν_{max} = 1613, 1589, 1508; HRMS: *m*/*z* (ES) 240.1003, $C_{13}H_{15}NNaO_2$ $[M+Na]^+$ requires 240.1000.

3-(1*H*-Pyrrol-1-yl)propanenitrile (240)[68]



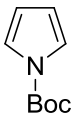
Based on a literature procedure,[68] 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, **5**) (0.15 mL, 1 mmol) was added to a solution of pyrrole (**236**) (1.39 mL, 20 mmol) and acrylonitrile (1.7 mL, 26 mmol) in a round-bottom flask. The solution was stirred at room temperature for 20 hours before being diluted with Et_2O and washed with NH_4Cl. The organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure to yield the title compound (2.15 g, 90%) as a pale yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 6.71 (2H, t, *J* = 2.0 Hz, C*H*N), 6.20 (2H, t, *J* = 2.0 Hz, C*H*CHN), 4.19 (2H, t, *J* = 6.8 Hz, NC*H*$_2$), 2.76 (2H, t, *J* = 6.8 Hz, C*H*$_2$CN); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 120.5, 117.3, 109.7, 45.2, 21.0.

1,2-Dimethyl-1*H*-pyrrole (241)[139]



Based on a literature procedure,[139] *N*-methylpyrrole (**167**) (0.90 mL, 10 mmol) and THF (10 mL) were added to a nitrogen purged three-neck round-bottom flask and cooled to –78 °C. ^{n}BuLi (2.5 M in hexanes, 4 mL, 10 mmol) was added dropwise and the solution was stirred overnight, allowing to warm slowly to room temperature. The solution was again cooled to –78 °C and methyl iodide (0.62 mL, 10 mmol) in THF (10 mL) was added in one portion. The reaction was stirred at –78 °C for four hours and was then allowed to warm slowly for three hours. The reaction was quenched by adding H_2O (20 mL) and was then extracted with Et_2O. The organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by Kugelrohr distillation (bp 140 °C), yielding the title compound (0.57 g, 60%) as a yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 6.56 (1H, t, *J* = 2.0 Hz, C*H*N), 6.05 (1H, t, *J* = 3.0 Hz, C*H*CHN), 5.91-5.88 (1H, m, C*H*CN), 3.54 (3H, s, NC*H*$_3$), 2.24 (3H, s, CC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 129.0, 121.0, 106.6, 106.5, 33.7, 12.0.

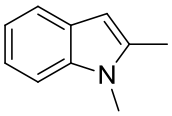
***t*-Butyl 1*H*-pyrrole-1-carboxylate (242)**[250]



Based on a literature procedure,[250] DMAP (**39**) (0.12 g, 1 mmol) and di-*t*-butyl dicarbonate (2.62 g, 12 mmol) were added to a solution of pyrrole (**236**) (0.69 mL, 10 mmol) in acetonitrile

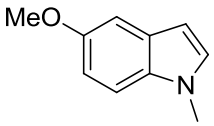
(10 mL) and the solution was stirred at room temperature for 24 hours. The reaction mixture was diluted with Et_2O and washed with $NaHCO_3$ and then brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petrol : EtOAc (99:1), R_f = 0.19), yielding the title compound (1.44 g, 86%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.24 (2H, t, *J* = 2.3 Hz, C*H*N), 6.22 (2H, t, *J* = 2.3 Hz, C*H*CHN), 1.60 (9H, s, C(C*H*$_3$)$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 149.1, 120.1, 112.0, 83.7, 28.1.

1,2-Dimethyl-1*H*-indole (253)[251]



Based on a literature procedure,[251] sodium hydride (60% dispersion in mineral oil, 0.44 g, 11 mmol) was added portionwise to a solution of 2-methylindole (1.31 g, 10 mmol) in anhydrous DMF (16 mL). The solution was stirred at room temperature for 30 minutes before cooling to 0 °C, when methyl iodide (0.68 mL, 11 mmol) was added. The reaction was stirred at 0 °C for 30 minutes before warming to room temperature and stirring overnight. The reaction was quenched by adding H_2O and was extracted with 1:1 hexane : Et_2O. The organics were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petrol : EtOAc (95:5), R_f = 0.60), yielding the title compound (0.84 g, 58%) as a peach coloured solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.54 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.27 (1H, d, *J* = 7.6 Hz, Ar*H*), 7.17 (1H, td, *J* = 7.0, 1.3 Hz, Ar*H*), 7.08 (1H, td, *J* = 7.8, 1.3 Hz, Ar*H*), 6.27 (1H, t, *J* = 0.9 Hz, C*H*C(CH$_3$)N), 3.68 (3H, s, NC*H*$_3$), 2.44 (3H, d, *J* = 0.9 Hz, CC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 137.5, 136.9, 128.1, 120.6, 119.7, 119.4, 108.8, 99.7, 29.5, 12.9.

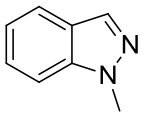
5-Methoxy-1-methyl-1*H*-indole (254)[252]



Based on a literature procedure,[251] sodium hydride (60% dispersion in mineral oil, 0.29 g, 7.1 mmol) was added portionwise to a solution of 5-methoxyindole (0.7 g, 4.8 mmol) in anhydrous DMF (9.6 mL). The solution was stirred at room temperature for 30 minutes before cooling to 0 °C, when methyl iodide (0.33 mL, 5.3 mmol) was added. The reaction was stirred at 0 °C for 30 minutes before warming to room temperature and stirring overnight. The reaction was quenched by adding H_2O and was extracted with 1:1 hexane : Et_2O. The organics were washed with H_2O,

dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petrol : EtOAc (90:10), R_f = 0.65), yielding the title compound (0.59 g, 76%) as a white crystalline solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.22 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.11 (1H, d, *J* = 2.3 Hz, Ar*H*), 7.03 (1H, d, *J* = 3.0 Hz, C*H*N), 6.90 (1H, dd, *J* = 8.8, 2.4 Hz, Ar*H*), 6.41 (1H, dd, *J* = 3.0, 0.8 Hz, C*H*CHN), 3.87 (3H, s, OCH_3), 3.78 (3H, s, NCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 154.1, 132.2, 129.3, 128.9, 111.9, 110.0, 102.6, 100.4, 55.9, 32.9; IR (film, cm^{-1}): ν_{max} = 1607, 1577, 1494, 1419; HRMS: *m*/*z* (ES) 162.0906, $C_{10}H_{12}NO$ $[M+H]^+$ requires 162.0919.

1-Methyl-1*H*-indazole (263)[253]



Based on a literature procedure,[251] sodium hydride (60% dispersion in mineral oil, 0.30 g, 7.5 mmol) was added portionwise to a solution of indazole (0.59 g, 5 mmol) in anhydrous DMF (10 mL). The solution was stirred at room temperature for 30 minutes before cooling to 0 °C, when methyl iodide (0.34 mL, 5.5 mmol) was added. The reaction was stirred at 0 °C for 30 minutes before warming to room temperature and stirring overnight. The reaction was quenched by adding H_2O and was extracted with 1:1 hexane : Et_2O. The organics were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by recrystallisation from Et_2O and petrol to yield the title compound (0.44 g, 67%) as a white solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.98 (1H, s, C*H*NN), 7.73 (1H, dt, *J* = 8.1 and 0.9 Hz, Ar*H*), 7.41-7.39 (2H, m, Ar*H*), 7.18-7.12 (1H, m, Ar*H*), 4.08 (3H, s, NCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 140.01, 132.82, 126.33, 124.14, 121.19, 120.55, 109.01, 35.62; IR (film, cm^{-1}): ν_{max} = 1612, 1500, 1467, 1409; HRMS: *m*/*z* (ES) 133.0760, $C_8H_9N_2$ $[M+H]^+$ requires 133.0766.

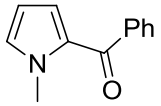
5.2.2 General Procedure for the Organocatalytic Friedel-Crafts Acylation

To a nitrogen purged Radleys carousel tube (150 × 24 mm fitted with gas-tight threaded PTFE caps with a suba-seal, sidearm and inlet valve) was added the appropriate *N*-protected pyrrole or indole (1 mmol), toluene (0.11 mL, 1 mmol), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, **6**) (0.018 mL, 0.15 mmol), and acyl chloride (1.2 mmol). The sealed carousel tube was then heated at 115 °C for four hours, before cooling to room temperature. The resulting mixture was diluted with CH_2Cl_2 and washed with 1M HCl followed by 1M NaOH, before being dried with $MgSO_4$, filtered, and concentrated under reduced pressure. Conversions were obtained by ^{1}H NMR

spectroscopic analysis of the crude reaction mixture using 2,5-dimethylfuran as an internal standard. The crude product was purified by either column chromatography or recrystallization.

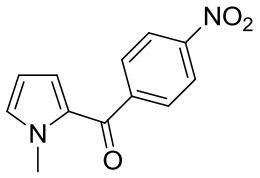
5.2.3 *C*2-Acyl Pyrrole Compound Data

(1-Methyl-1*H*-pyrrol-2-yl)(phenyl)methanone (219)[110]



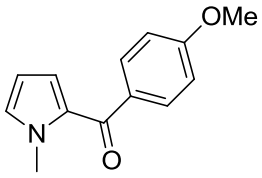
N-methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and benzoyl chloride (**213**) (0.14 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : Et_2O (90:10), R_f = 0.69), yielding the title compound (0.14 g, 73%) as a colourless oil with spectroscopic data in accordance to the literature.[110] ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.82-7.79 (2H, m, Ar*H*), 7.56-7.42 (3H, m, Ar*H*), 6.92 (1H, app. t, *J* = 2.0 Hz, C*H*N), 6.74 (1H, dd, *J* = 4.1, 1.7 Hz, CC*H*), 6.16 (1H, dd, *J* = 4.1, 2.5 Hz, C*H*CHN), 4.04 (3H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 186.3, 140.0, 131.6, 131.5, 130.6, 129.3, 128.2, 123.0, 108.2, 37.5; IR (film, cm^{-1}): ν_{max} = 1622 (C=O); HRMS: *m*/*z* (ES) 186.0899, $C_{12}H_{12}NO$ $[M+H]^+$ requires 186.0919.

(1-Methyl-1*H*-pyrrol-2-yl)(4-nitrophenyl)methanone (220)[107]



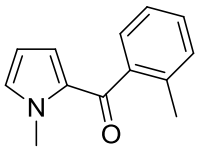
N-Methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and 4-nitrobenzoyl chloride (**214**) (0.22 g, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : EtOAc (90:10), R_f = 0.20), yielding the title compound (0.17 g, 74%) as yellow crystals with spectroscopic data in accordance with the literature.[107] mp: 151-153 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 8.31 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.92 (2H, d, *J* = 9.0 Hz, Ar*H*), 6.99 (1H, app. t, *J* = 1.8 Hz, C*H*N), 6.68 (1H, dd, *J* = 4.2, 1.6 Hz, CC*H*), 6.19 (1H, dd, *J* = 4.2, 2.5 Hz, C*H*CHN), 4.06 (3H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 183.8, 149.4, 145.5, 132.9, 130.0, 123.8, 123.5, 109.0, 37.7; IR (film, cm^{-1}): ν_{max} = 1623 (C=O); HRMS: *m*/*z* (ES) 231.0744, $C_{12}H_{11}N_2O_3$ $[M+H]^+$ requires 231.0770.

(4-Methoxyphenyl)(1-methyl-1*H*-pyrrol-2-yl)methanone (221)



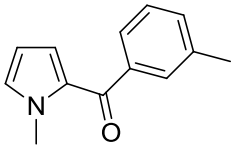
N-Methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and 4-methoxybenzoyl chloride (**215**) (0.16 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : Et_2O (90:10), R_f = 0.09), yielding the title compound (0.14 g, 66%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.86-7.81 (2H, m, Ar*H*), 6.97-6.92 (2H, m, Ar*H*), 6.89 (1H, app. t, *J* = 2.0 Hz, C*H*N), 6.72 (1H, dd, *J* = 4.0, 1.7 Hz, CC*H*), 6.15 (1H, dd, *J* = 4.0, 2.5 Hz, C*H*CHN), 4.01 (3H, s, NCH_3), 3.87 (3H, s, OCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 185.3, 162.6, 132.6, 131.6, 130.8, 122.0, 113.4, 108.0, 55.5, 37.3; IR (film, cm^{-1}): ν_{max} = 1623 (C=O); HRMS: *m*/*z* (ES) 216.1004, $C_{13}H_{14}NO_2$ $[M+H]^+$ requires 216.1025.

(1-Methyl-1*H*-pyrrol-2-yl)(*o*-tolyl)methanone (222)



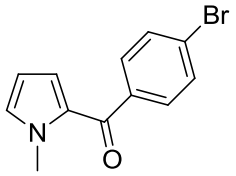
N-Methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and *o*-toluoyl chloride (**216**) (0.16 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : Et_2O (95:5), R_f = 0.19), yielding the title compound (0.13 g, 63%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.30-7.21 (2H, m, Ar*H*), 7.17-7.09 (2H, m, Ar*H*), 6.80 (1H, app. t, *J* = 2.0 Hz, C*H*N), 6.39 (1H, dd, *J* = 4.1, 1.8 Hz, CC*H*), 6.00 (1H, dd, *J* = 4.1, 2.6 Hz, C*H*CHN), 3.99 (3H, s, NCH_3), 2.28 (3H, s, CCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 188.3, 140.3, 136.2, 131.9, 131.5, 130.8, 129.5, 128.2, 124.9, 123.7, 108.3, 37.6, 19.7; IR (film, cm^{-1}): ν_{max} = 1619 (C=O); HRMS: *m*/*z* (ES) 200.1072, $C_{13}H_{14}NO$ $[M+H]^+$ requires 200.1075.

(1-Methyl-1*H*-pyrrol-2-yl)(*m*-tolyl)methanone (223)



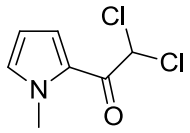
N-Methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and *m*-toluoyl chloride (**217**) (0.16 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : Et_2O (90:10), R_f = 0.25), yielding the title compound (0.12 g, 58%) as a yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.62-7.56 (2H, m, Ar*H*), 7.36-7.30 (2H, m, Ar*H*), 6.91 (1H, app. t, *J* = 2.0 Hz, C*H*N), 6.74 (1H, dd, *J* = 4.0, 1.7 Hz, CC*H*), 6.16 (1H, dd, *J* = 4.0, 2.5 Hz, C*H*CHN), 4.04 (3H, s, NCH_3), 2.42 (3H, s, CCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 186.5, 140.1, 137.9, 132.2, 131.5, 130.8, 129.8, 128.0, 126.5, 122.9, 108.1, 37.5, 21.5; IR (film, cm^{-1}): ν_{max} = 1623 (C=O); HRMS: *m*/*z* (ES) 200.1068, $C_{13}H_{14}NO$ $[M+H]^+$ requires 200.1075.

(4-Bromophenyl)(1-methyl-1*H*-pyrrol-2-yl)methanone (224)



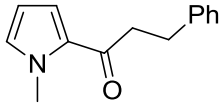
N-Methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and 4-bromobenzoyl chloride (**218**) (0.22 g, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : Et_2O (95:5), R_f = 0.24), yielding the title compound (0.18 g, 70%) as a white solid. mp: 72-73 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.67 (2H, dt, *J* = 8.6, 2.0 Hz, Ar*H*), 7.58 (2H, dt, *J* = 8.6, 2.0 Hz, Ar*H*), 6.93 (1H, app. t, *J* = 2.0 Hz, C*H*N), 6.70 (1H, dd, *J* = 4.1, 1.7 Hz, CC*H*), 6.16 (1H, dd, J = 4.2, 2.5 Hz, C*H*CHN), 4.02 (3H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 184.9, 138.8, 131.9, 131.4, 130.8, 130.3, 126.2, 122.9, 108.4, 37.5; IR (film, cm^{-1}): ν_{max} = 1624 (C=O); HRMS: *m*/*z* (ES) 264.0027, $C_{12}H_{11}BrNO$ [M+H] requires 264.0024.

2,2-Dichloro-1-(1-methyl-1*H*-pyrrol-2-yl)ethanone (231)[254]



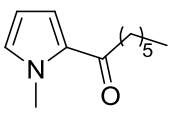
N-Methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and dichloroacetyl chloride (**225**) (0.12 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. No purification was required and the title compound (0.15 g, 80%) was obtained as a yellow solid with spectroscopic data in accordance with the literature.[254] mp: 65-66 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.14 (1H, dd, *J* = 4.3, 1.5 Hz, CC*H*), 6.98 (1H, app. t, *J* = 1.7 Hz, C*H*N), 6.58 (1H, s, C*H*Cl_2), 6.23 (1H, dd, *J* = 4.3, 2.4 Hz, C*H*CHN), 3.98 (3H, s, NCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 176.7, 134.0, 125.3, 121.3, 109.4, 68.1, 38.0; IR (film, cm^{-1}): ν_{max} = 1654 (C=O); HRMS: *m*/*z* (ES) 191.9969, $C_7H_8Cl_2NO$ $[M+H]^+$ requires 191.9983.

1-(1-Methyl-1*H*-pyrrol-2-yl)-3-phenylpropan-1-one (232)[255]



N-Methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and hydrocinnamoyl chloride (**226**) (0.18 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : Et_2O (90:10), R_f = 0.24), yielding the title compound (0.15 g, 70%) as a yellow oil with spectroscopic data in accordance with the literature.[255] ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.25-7.08 (5H, m, Ar*H*), 6.86 (1H, dd, *J* = 4.1, 1.7 Hz, CC*H*), 6.71 (1H, app. t, *J* = 1.9 Hz, C*H*N), 6.02 (1H, dd, *J* = 4.1, 2.5 Hz, C*H*CHN), 3.86 (3H, s, CH_3), 3.05-3.00 (2H, m, CH_2Ph), 2.96-2.90 (2H, m, CH_2CH_2Ph); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 190.3, 141.6, 131.1, 130.7, 128.6, 128.5, 126.1, 119.1, 108.0, 40.8, 37.8, 31.0; IR (film, cm^{-1}): ν_{max} = 1643 (C=O); HRMS: *m*/*z* (ES) 214.1217, $C_{14}H_{16}NO$ $[M+H]^+$ requires 214.1232.

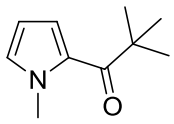
1-(1-Methyl-1*H*-pyrrol-2-yl)heptan-1-one (233)[256]



N-Methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and heptanoyl chloride (**227**) (0.19 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : Et_2O (90:10), R_f = 0.38), yielding the title compound (0.16 g, 82%)

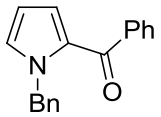
as a yellow oil with spectroscopic data in accordance with the literature.[256] ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 6.95 (1H, dd, *J* = 4.1, 1.7 Hz, CC*H*), 6.78 (1H, app. t, *J* = 2.0 Hz, C*H*N), 6.11 (1H, dd, *J* = 4.1, 2.5 Hz, C*H*CHN), 3.94 (3H, s, NCH_3), 2.75 (2H, t, *J* = 7.5 Hz, COCH_2), 1.69 (2H, app. p, *J* = 7.5 Hz, $COCH_2CH_2$), 1.38-1.26 (6H, m, $(CH_2)_3CH_3$), 0.89 (3H, t, *J* = 6.8 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 191.9, 130.9, 119.0, 107.9, 39.3, 37.8, 31.8, 29.3, 25.4, 22.7, 14.2; IR (film, cm^{-1}): ν_{max} = 1646 (C=O); HRMS: *m*/*z* (ES) 216.1363, $C_{12}H_{19}NNaO$ $[M+Na]^+$ requires 216.1364.

2,2-Dimethyl-1-(1-methyl-1*H*-pyrrol-2-yl)propan-1-one (235)[257]



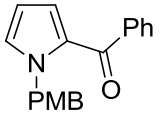
N-Methylpyrrole (**167**) (0.09 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and pivaloyl chloride (**230**) (0.15 mL, 1.2 mmol) were heated at 115 °C for six hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : Et_2O (90:10), R_f = 0.36), yielding the title compound (0.08 g, 49%) as a colourless oil with spectroscopic data in accordance with the literature.[257] ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.03 (1H, dd, *J* = 4.2, 1.6 Hz, CC*H*), 6.74 (1H, t, *J* = 2.0 Hz, C*H*N), 6.11 (1H, dd, *J* = 4.2, 2.5 Hz, C*H*CHN), 3.90 (3H, s, NCH_3), 1.36 (9H, s, $C(CH_3)_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 198.0, 129.9, 128.7, 118.8, 107.2, 43.9, 38.7, 29.0; IR (film, cm^{-1}): ν_{max} = 1636 (C=O); HRMS: *m*/*z* (ES) 166.1225, $C_{10}H_{16}NO$ $[M+H]^+$ requires 166.1232.

(1-Benzyl-1*H*-pyrrol-2-yl)(phenyl)methanone (245)



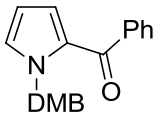
N-Benzylpyrrole (**237**) (0.15 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and benzoyl chloride (**213**) (0.14 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (hexane : Et_2O (95:5), R_f = 0.20), yielding the title compound (0.15 g, 56%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.70-7.66 (2H, m, Ar*H*), 7.44-7.29 (3H, m, Ar*H*), 7.23-7.08 (5H, m, Ar*H*), 6.91 (1H, dd, *J* = 2.5, 1.8 Hz, C*H*N), 6.68 (1H, dd, *J* = 4.1, 1.7 Hz, CC*H*), 6.11 (1H, dd, *J* = 4.1, 2.5 Hz, C*H*CHN), 5.57 (2H, s, CH_2Ph); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 186.3, 140.0, 138.4, 131.5, 131.0, 130.3, 129.3, 128.7, 128.1, 127.6, 127.3, 123.6, 108.8, 52.5; IR (film, cm^{-1}): ν_{max} = 1616 (C=O); HRMS: *m*/*z* (ES) 262.1227, $C_{18}H_{16}NO$ $[M+H]^+$ requires 262.1231.

(1-(4-Methoxybenzyl)-1*H*-pyrrol-2-yl)(phenyl)methanone (246)



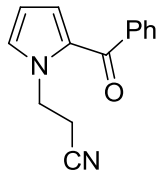
1-(4-Methoxybenzyl)-1*H*-pyrrole (**238**) (0.19 g, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and benzoyl chloride (**213**) (0.14 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (petrol : EtOAc (95:5), R_f = 0.27), yielding the title compound (0.23 g, 79%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.80-7.77 (2H, m, Ar*H*), 7.55-7.40 (3H, m, Ar*H*), 7.18 (2H, d, *J* = 8.7 Hz, Ar*H*), 7.01 (1H, app. t, *J* = 2.0 Hz, C*H*N), 6.85 (2H, d, *J* = 8.7 Hz, Ar*H*), 6.76 (1H, dd, *J* = 4.0, 1.7 Hz, CC*H*), 6.19 (1H, dd, *J* = 4.0, 2.6 Hz, C*H*CHN), 5.60 (2H, s, CH_2Ar), 3.78 (3H, s, OCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 186.3, 159.2, 140.1, 131.5, 130.7, 130.4, 130.2, 129.4, 129.0, 128.1, 123.7, 114.2, 108.7, 55.4, 52.0; IR (film, cm^{-1}): ν_{max} = 1624 (C=O); HRMS: *m*/*z* (ES) 292.1323, $C_{19}H_{18}NO_2$ $[M+H]^+$ requires 292.1338.

(1-(2,4-Dimethoxybenzyl)-1H-pyrrol-2-yl)(phenyl)methanone (247)



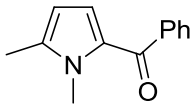
1-(2,4-Dimethoxybenzyl)-1*H*-pyrrole (**239**) (0.12 g, 0.5 mmol), toluene (0.05 mL, 0.5 mmol), DBN (**6**) (0.009 mL, 0.075 mmol), and benzoyl chloride (**213**) (0.08 mL, 0.7 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (petrol : EtOAc (90:10), R_f = 0.32), yielding the title compound (0.10 g, 62%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.81-7.78 (2H, m, Ar*H*), 7.55-7.40 (3H, m, Ar*H*), 7.04-7.01 (2H, m, Ar*H*, C*H*N), 6.72 (1H, dd, *J* = 4.0, 1.7 Hz, CC*H*), 6.46 (1H, d, *J* = 2.4 Hz, Ar*H*), 6.40 (1H, dd, *J* = 8.3, 2.4 Hz, Ar*H*), 6.14 (1H, dd, *J* = 4.0, 2.5 Hz, C*H*CHN), 5.62 (2H, s, CH_2Ar), 3.82 (3H, s, OCH_3), 3.78 (3H, s, CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 186.4, 160.7, 158.3, 140.3, 133.9, 131.4, 131.3, 130.3, 130.1, 129.4, 128.6, 128.1, 123.5, 119.3, 108.2, 104.2, 98.5, 55.5, 55.4, 47.1; IR (film, cm^{-1}): ν_{max} = 1691 (C=O); HRMS: *m*/*z* (ES) 322.1434, $C_{20}H_{20}NO_3$ $[M+H]^+$ requires 322.1443.

3-(2-Benzoyl-1*H*-pyrrol-1-yl)propanenitrile (248)



3-(1*H*-Pyrrol-1-yl)propanenitrile (**240**) (0.12 g, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and benzoyl chloride (**213**) (0.14 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (petrol : EtOAc (80:20), R_f = 0.32), yielding the title compound (0.16 g, 73%) as a colourless solid. mp: 88-89 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.80-7.76 (2H, m, Ar*H*), 7.59-7.44 (3H, m Ar*H*), 7.11 (1H, dd, *J* = 2.4, 1.8 Hz, C*H*N), 6.84 (1H, dd, *J* = 4.1, 1.7 Hz, CC*H*), 6.25 (1H, dd, *J* = 4.1, 2.6 Hz, C*H*CHN), 4.62 (2H, t, *J* = 6.3 Hz, NCH_2), 3.03 (2H, t, *J* = 6.3 Hz, CH_2CN); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 186.4, 139.6, 131.8, 131.6, 129.7, 129.3, 128.3, 124.5, 117.7, 109.5, 45.7, 20.6; IR (film, cm^{-1}): ν_{max} = 2253 (CN), 1608 (C=O); HRMS: *m*/*z* (ES) 225.1030, $C_{14}H_{13}N_2O$ $[M+H]^+$ requires 225.1028.

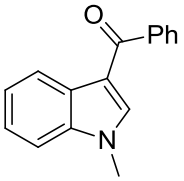
(1,5-Dimethyl-1*H*-pyrrol-2-yl)(phenyl)methanone (249)



1,2-Dimethyl-1*H*-pyrrole (**241**) (0.10 g, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and benzoyl chloride (**213**) (0.14 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (petrol : EtOAc (90:10), R_f = 0.42), yielding the title compound (0.13 g, 63%) as a pale yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.80-7.76 (2H, m, Ar*H*), 7.53-7.40 (3H, m, Ar*H*), 6.65 (1H, d, *J* = 4.0 Hz, C(CH_3)CHC*H*), 5.96 (1H, dd, *J* = 4.0, 0.6 Hz), 3.94 (3H, s, NCH_3), 2.30 (3H, s, CCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 185.6, 140.6, 139.6, 131.1, 130.6, 129.2, 128.0, 123.4, 108.4, 33.0, 12.7; IR (film, cm^{-1}): ν_{max} = 1615 (C=O); HRMS: *m*/*z* (ES) 200.1072, $C_{13}H_{14}NO$ $[M+H]^+$ requires 200.1075.

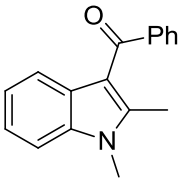
5.2.4 *C*2-Acyl Indole Compound Data

(1-Methyl-1*H*-indol-3-yl)(phenyl)methanone (256)



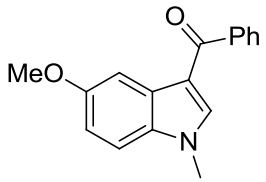
1-Methyl-1*H*-indole (**252**) (0.12 mL, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and benzoyl chloride (**213**) (0.14 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (dichloromethane (neat), R_f = 0.21), yielding the title compound (0.13 g, 54%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 8.46-8.41 (1H, m, Ph-*H*), 7.82 (2H, app. dt, *J* = 6.5, 1.7 Hz, indole-H_2), 7.56-7.45 (4H, m, indole-H_2, Ph-*H*, C*H*N), 7.39-7.33 (3H, m, Ph-H_3), 3.85 (3H, s, NCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 190.9, 141.0, 138.0, 137.7, 131.2, 128.8, 128.4, 127.3, 123.8, 122.9, 122.8, 115.7, 109.7, 33.6; IR (film, cm^{-1}): ν_{max} = 1611 (C=O); HRMS: *m*/*z* (ES) 236.1073, $C_{16}H_{14}NO$ $[M+H]^+$ requires 236.1075.

(1,2-Dimethyl-1*H*-indol-3-yl)(phenyl)methanone (257)



1,2-Dimethyl-1*H*-indole (**253**) (0.15 g, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and benzoyl chloride (**213**) (0.14 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (petrol : EtOAc (80:20), R_f = 0.35), yielding the title compound (0.22 g, 88%) as a peach coloured solid. mp: 139-141 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.76 (2H, dt, *J* = 6.9, 1.6 Hz, Ar*H*), 7.55 (1H, tt, *J* = 7.3, 1.4 Hz, Ar*H*), 7.48-7.42 (2H, m, Ar*H*), 7.34-7.30 (2H, m, Ar*H*), 7.22 (1H, td, *J* = 7.2, 1.2 Hz, Ar*H*), 7.07 (1H, td, *J* = 7.2, 1.0 Hz, Ar*H*), 3.74 (3H, s, NCH_3), 2.59 (3H, s, CCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 193.0, 144.8, 141.6, 136.7, 131.6, 129.2, 128.4, 127.2, 122.2, 121.5, 121.1, 113.8, 109.3, 29.8, 12.7; IR (film, cm^{-1}): ν_{max} = 1608 (C=O); HRMS: *m*/*z* (ES) 250.1240, $C_{17}H_{16}NO$ $[M+H]^+$ requires 250.1232.

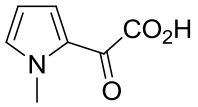
(5-Methoxy-1-methyl-1*H*-indol-3-yl)(phenyl)methanone (258)



5-Methoxy-1-methyl-1*H*-indole (**254**) (0.16 g, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and benzoyl chloride (**213**) (0.14 mL, 1.2 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (petrol : EtOAc (80:20), R_f = 0.26), yielding the title compound (0.10 g, 40%) as a pale yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.88 (1H, d, *J* = 2.4 Hz, Ar*H*), 7.70 (2H, dt, *J* = 6.5, 1.5 Hz, Ar*H*), 7.46-7.35 (4H, m, Ar*H*, C*H*N), 7.14 (1H, d, *J* = 8.9 Hz, Ar*H*), 6.88 (1H, dd, *J* = 8.9, 2.5 Hz, Ar*H*), 3.82 (3H, s, NCH_3), 3.68 (3H, s, OCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 191.0, 156.7, 141.1, 138.1, 132.6, 131.1, 128.7, 128.4, 128.1, 115.3, 114.3, 110.6, 104.0, 55.9, 33.8; IR (film, cm^{-1}): ν_{max} = 1612 (C=O); HRMS: *m*/*z* (ES) 266.1192, $C_{17}H_{16}NO_2$ $[M+H]^+$ requires 266.1181.

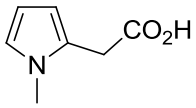
5.2.5 Tolmetin Synthesis Compound Data

2-(1-Methyl-1*H*-pyrrol-2-yl)-2-oxoacetic acid (264)[140]



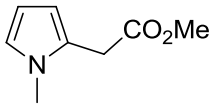
Based on a literature procedure,[140] oxalyl chloride (4.30 mL, 50 mmol) and CH_2Cl_2 (20 mL) were added to a three-neck round-bottom flask and cooled to -10 °C under a nitrogen atmosphere. *N*-Methylpyrrole (**167**) (4.44 mL, 50 mmol) in CH_2Cl_2 (40 mL) was added dropwise *via* a dropping funnel, maintaining the temperature below 0 °C. The resulting solution was stirred at 0 °C for one hour before sufficient 20% KOH(aq) was added to make the solution pH 10. The solution was stirred for 30 minutes and then diluted with H_2O. The two layers were separated and the aqueous layer extracted with CH_2Cl_2. To the combined organic layers was added 20% H_2SO_4(aq) until a white precipitate formed and the solution was stirred for 30 minutes. The solid was filtered, washing with cold H_2O, before being dried under reduced pressure to yield the title compound (5.28 g, 69%) as a pale yellow solid. mp: 140-141 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 8.05 (1H, dd, *J* = 4.4, 1.6 Hz, CC*H*), 7.10 (1H, app. t, *J* = 1.8 Hz, C*H*N), 6.28 (1H, dd, *J* = 4.4, 2.4 Hz, C*H*CHN), 3.99 (3H, s, NCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.5, 160.5, 136.7, 128.9, 126.7, 111.1, 38.3; IR (film, cm^{-1}): ν_{max} = 2739 (O-H), 1718 (C=O); HRMS: *m*/*z* (ES) 154.0503, $C_7H_8NO_3$ $[M+H]^+$ requires 154.0504.

2-(1-Methyl-1*H*-pyrrol-2-yl)acetic acid (265)[140]



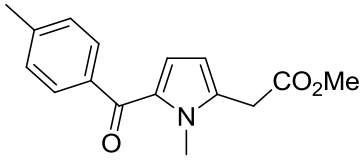
Based on a literature procedure,[140] 2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoacetic acid (**264**) (3.08 g, 20 mmol), hydrazine monohydrate (2.00 mL, 40 mmol), and 20% KOH(aq) (40 mL) were added to a two-neck round-bottom flask fitted with a reflux condenser under a nitrogen atmosphere. The resulting solution was heated at 100 °C for eight hours. After cooling to room temperature, 2M HCl was added to make the solution pH 2. The mixture was extracted with CH_2Cl_2 and the organics were washed with H_2O, before drying with $MgSO_4$ and filtering. The solvent was removed under reduced pressure and the crude recrystallized from Et_2O and petrol to yield the title compound (1.88 g, 68%) as a yellow solid. mp: 107-108 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 6.61 (1H, app. t, *J* = 2.3 Hz, C*H*N), 6.10-6.06 (2H, m, C*H*CHN, CC*H*), 3.67 (2H, s, C*H*$_2$CO$_2$H), 3.59 (3H, s, NC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 176.9, 124.1, 122.9, 109.3, 107.3, 34.0, 32.4; IR (film, cm^{-1}): ν_{max} = 2919 (O-H), 1688 (C=O); HRMS: *m*/*z* (ES) 140.0712, $C_7H_{10}NO_2$ $[M+H]^+$ requires 140.0712.

Methyl 2-(1-methyl-1*H*-pyrrol-2-yl)acetate (266)[140]



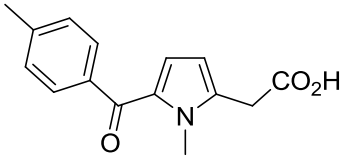
2-(1-Methyl-1*H*-pyrrol-2-yl)acetic acid (**265**) (1.14 g, 8 mmol) and *p*-toluenesulfonic acid (0.47 g, 2 mmol) were added to a two-neck round-bottom flask fitted with a reflux condenser under a nitrogen atmosphere. MeOH (20 mL) was added and the reaction refluxed at 70 °C for eight hours. After cooling to room temperature, the methanol was removed under reduced pressure and the crude was diluted with CH_2Cl_2 before being washed with brine. The organics were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was purified by flash column chromatography (petrol : EtOAc (90:10), R_f = 0.38), yielding the title compound (0.98 g, 80%) as a colourless oil with spectroscopic data in accordance with the literature.[140] ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 6.60 (1H, app. t, *J* = 2.1 Hz, C*H*N), 6.09-6.04 (2H, m, CC*H*, C*H*CHN), 3.71 (3H, s, NC*H*$_3$), 3.64 (2H, s, C*H*$_2$CO$_2$Me), 3.58 (3H, s, OC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.1, 124.9, 122.7, 108.9, 107.1, 52.2, 34.0, 32.6; IR (film, cm^{-1}): ν_{max} = 1733 (C=O); HRMS: *m*/*z* (ES) 154.0862, $C_8H_{12}NO_2$ $[M+H]^+$ requires 154.0868.

Methyl 2-(1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrol-2-yl)acetate (268)[140]



Methyl 2-(1-methyl-1*H*-pyrrol-2-yl)acetate (**266**) (0.46 g, 3 mmol), toluene (0.33 mL, 3 mmol), DBN (**6**) (0.054 mL, 0.45 mmol), and *p*-toluoyl chloride (**267**) (0.48 mL, 3.6 mmol) were heated at 115 °C for four hours according to the general procedure. The crude product was purified by flash column chromatography (petrol : EtOAc (80:20), R_f = 0.38) yielding the title compound (0.54 g, 66%) as a pale yellow solid with spectroscopic data in accordance with the literature.[140] mp: 116-117 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.63 (2H, d, *J* = 8.1 Hz, Ar*H*), 7.16 (2H, d, *J* = 7.9 Hz, Ar*H*), 6.59 (1H, d, *J* = 4.0 Hz, C*H*CCO), 6.02 (1H, d, *J* = 4.0 Hz, C*H*CCH$_2$), 3.86 (3H, s, NC*H*$_3$), 3.66 (3H, s, OC*H*$_3$), 3.64 (2H, s, C*H*$_2$CO$_2$Me), 2.34 (3H, s, CC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 186.0, 169.9, 142.0, 137.4, 134.5, 131.6, 130.3, 129.5, 129.3, 128.8, 122.4, 109.6, 52.6, 33.3, 32.8,, 21.6; IR (film, cm^{-1}): ν_{max} = 1722 (C=O), 1622 (C=O); HRMS: *m*/*z* (ES) 272.1277, $C_{16}H_{18}NO_3$ $[M+H]^+$ requires 272.1287.

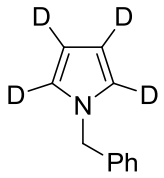
2-(1-Methyl-5-(4-methylbenzoyl)-1*H*-pyrrol-2-yl)acetic acid, Tolmetin (165)[140]



Methyl 2-(1-methyl-5-(4-methylbenzoyl)-1*H*-pyrrol-2-yl)acetate (**268**) (0.40 g, 1.5 mmol), H_2O (4.2 mL), and 2.5M NaOH (aq) (0.72 mL, 1.8 mmol) were added to a round-bottom flask and stirred at room temperature for 48 hours, until all the solid had dissolved. The solution was acidified with 2M HCl until a precipitate was formed. The mixture was diluted with CH_2Cl_2 and the layers were separated, washing the organics with brine, before drying with $MgSO_4$, filtering, and concentrating under reduced pressure. The crude was purified by stirring with Et_2O and filtering, yielding the title compound (0.30 g, 78%) as a white solid with spectroscopic data in accordance with the literature.[140] mp: 156-157 °C; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.70 (2H, d, *J* = 7.9 Hz, Ar*H*), 7.23 (2H, d, *J* = 7.9 Hz, Ar*H*), 6.67 (1H, d, *J* = 3.8 Hz, C*H*CCO), 6.12 (1H, d, *J* = 3.7 Hz, C*H*CCH$_2$), 3.93 (3H, s, NC*H*$_3$), 3.75 (2H, s, C*H*$_2$CO$_2$H), 2.41 (3H, s, CC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 186.3, 175.1, 142.2, 137.2, 133.9, 131.7, 129.6, 128.9, 122.6, 109.9, 33.4, 32.7, 21.7; IR (film, cm^{-1}): ν_{max} = 3199 (O-H), 1731 (C=O), 1698 (C=O); HRMS: *m*/*z* (ES) 258.1126, $C_{15}H_{16}NO_3$ $[M+H]^+$ requires 258.1130.

5.2.6 Kinetics Experiments

***N*-Benzyl-D_4-pyrrole (273)**



Firstly, D_5-pyrrole (**272**) was synthesised in accordance to a literature procedure.[141] Pyrrole (**236**) (2 mL, 29 mmol), acetic acid-d_1 (1.83 mL, 32 mmol), and D_2O (4 mL) were equilibrated at room temperature for eight hours in the absence of light. Anhydrous CH_2Cl_2 was added and the solution neutralised with K_2CO_3. The layers were then separated and the organics dried over $MgSO_4$, filtered, and the solvent was allowed to evaporate slowly. The procedure was then repeated.

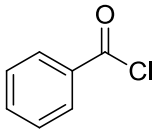
N-Benzyl-D_4-pyrrole (**273**) was then synthesised based on the literature procedure used previously.[137] Sodium hydride (60% dispersion in mineral oil, 0.17 g, 4.13 mmol) was added to anhydrous DMF (3.75 mL) in a nitrogen purged two-neck round-bottom flask. The solution was cooled to 0 °C before pyrrole-d_5 (**272**) (0.27 g, 3.75 mmol) in anhydrous DMF (1 mL) was added dropwise. The solution was allowed to warm to room temperature and was stirred for 30 minutes before cooling back to 0 °C and benzyl bromide (0.45 mL, 3.75 mmol) was added dropwise. The solution was again allowed to warm to room temperature and was stirred for one hour. The solution was then added to H_2O and extracted with 1:1 hexane : Et_2O. The combined organic layers were washed with H_2O before drying over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (petrol : ethyl acetate (95:5), R_f = 0.65) yielding the title compound (0.50 g, 83%) as a colourless oil with 85% deuterium incorporation, as determined by analysis of the ^{1}H NMR spectra. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.40-7.29 (3H, m, Ar*H*), 7.15-7.12 (2H, m, Ar*H*), 5.09 (2H, s, NCH_2Ph); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 138.3, 128.8, 127.8, 127.1, 53.4.

Kinetic Experiments

N-Benzyl-D_4-pyrrole (**273**) (0.16 g, 1 mmol), toluene (0.11 mL, 1 mmol), DBN (**6**) (0.018 mL, 0.15 mmol), and benzoyl chloride (**213**) (0.14 mL, 1.2 mmol) were heated at 115 °C according to the general procedure. Aliquots of 0.01 mL were taken every hour up to 6 hours and analysed using ^{1}H NMR. The procedure was then repeated with *N*-benzylpyrrole (**237**) (0.16 g, 1 mmol). Comparison of the data showed essentially no difference in the rate of acylation between the deuterated and non-deuterated pyrroles, suggesting that re-aromatisation is not the rate determining step.

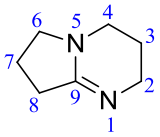
5.2.7 *N*-Benzoyl-DBN Intermediate Data

Benzoyl chloride (213)



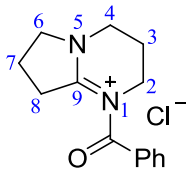
Commercially available benzoyl chloride (**213**) was analysed as a colourless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 8.13 (2H, dd, *J* = 8.4, 1.2 Hz, *o*-Ar*H*), 7.69 (1H, tt, *J* = 7.4, 1.2 Hz, *p*-Ar*H*), 7.52 (2H, dd, *J* = 8.3, 7.6 Hz, *m*-Ar*H*); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 168.6, 135.5, 133.4, 131.6, 129.1. IR (film, cm^{-1}): ν_{max} = 1770 (C=O), 1730, 1595, 1582.

1,5-Diazabicyclo[4.3.0]non-5-ene (DBN, 6)



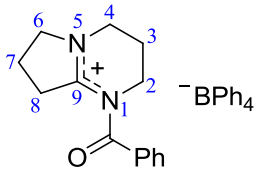
Commercially available DBN (**6**) was analysed as a colourless oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 3.27 (2H, t, *J* = 5.5 Hz, *H*^{2}), 3.21 (2H, t, *J* = 6.8 Hz, *H*^{6}), 3.12 (2H, t, *J* = 6.0 Hz, *H*^{4}), 2.38 (2H, t, *J* = 7.8 Hz, *H*^{8}), 1.86 (2H, p, *J* = 7.3 Hz, *H*^{7}), 1.72 (2H, p, *J* = 5.8 Hz, *H*^{3}); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 160.7 (*C*^{9}), 51.5 (*C*^{6}), 44.1 (*C*^{2}), 43.2 (*C*^{4}), 31.5 (*C*^{8}), 20.9 (*C* ^{3}), 19.7 (*C* ^{7}).

***N*-Benzoyl-DBN·Cl (269)**



Benzoyl chloride (**213**) (0.12 mL, 1 mmol) was added dropwise to a solution of DBN (**6**) (0.12 mL, 1 mmol) in $CDCl_3$. The solution turns yellow upon the addition of benzoyl chloride; after stirring at room temperature for two hours the colour had dissipated and complex **269** was formed in quantitative yield, as shown by ^{1}H NMR spectroscopy. The solution can be concentrated under reduced pressure to give a hygroscopic pale yellow powder. ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 7.88-7.86 (2H, m, *o*-Ar*H*), 7.50-7.45 (1H, m, *p*-Ar*H*), 7.39-7.36 (2H, m, *m*-Ar*H*), 3.96 (2H, t, *J* = 7.5 Hz, *H*^{6}), 3.92-3.89 (2H, m, *H*^{2}), 3.77-3.73 (2H, br. s, *H*^{4}), 3.39-3.33 (2H, m, *H*^{8}), 2.25-2.17 (2H, m, *H*^{7}), 2.15-2.10 (2H, m, *H*^{3}); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ_C = 170.9, 167.9, 133.5, 131.2, 129.6, 128.9, 55.4, 46.4, 44.6, 34.3, 19.7, 18.6; IR (film, cm^{-1}): ν_{max} = 1709 (C=O), 1679, 1644, 1598; HRMS: *m*/*z* (ES) 229.1336, $C_{14}H_{16}N_2O$ [M-H]$^{+}$ requires 229.1341.

***N*-Benzoyl-DBN·BPh_4 (275)**



Based on a literature procedure,[142] sodium tetraphenylborate (0.34 g, 1 mmol) was added to a 2-neck round bottom flask and placed under a nitrogen atmosphere. Dry acetonitrile (5 mL) and benzoyl chloride (**213**) (0.12 mL, 1.04 mmol) were added and the resulting solution cooled to 0 °C. DBN (**6**) (0.12 mL, 1 mmol) was added dropwise and the solution stirred for one hour. The stirring was stopped and the NaCl precipitate allowed to settle, before the yellow solution was removed using a filter cannula. The solvent was removed under reduced pressure to give a thick yellow oil, which was re-dissolved in acetonitrile and carefully layered with hexane. The layers were allowed to mix slowly before the mixture was transferred to a freezer, which allowed white crystals of *N*-acyl-DBN·BPh_4 (**275**) to form.

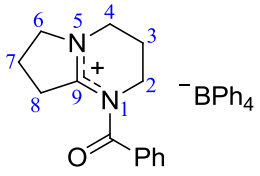
5.3 *N*-Acyl DBN·BPh_4 Salt Acylations

5.3.1 General Procedure for the Synthesis of *N*-Acyl DBN·BPh_4 Salts

Sodium tetraphenylborate (1 equiv.) is added to a round-bottom flask and purged with nitrogen. Dry acetonitrile (to make a 0.2 M solution of $NaBPh_4$) and the appropriate acyl chloride (1.04 equiv.) are added and the resulting solution is cooled to 0 °C. DBN (**6**) (1 equiv.) is added dropwise and a white precipitate of sodium chloride begins to form. The reaction is left to stir for one hour before being warmed to room temperature and filtered through a pad of Celite®, washing thoroughly with acetonitrile. The filtrate is concentrated under reduced pressure and the resulting *N*-acetyl-DBN salt is purified by recrystallisation from dichloromethane and hexane.

5.3.2 *N*-Acyl DBN·BPh_4 Salts Compound Data

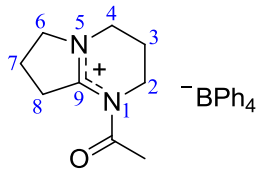
***N*-Benzoyl DBN BPh_4 (275)**



DBN (**6**) (1.85 mL, 15 mmol) was added dropwise to a solution of sodium tetraphenylborate (5.13 g, 15 mmol) and benzoyl chloride (**213**) (1.81 mL, 15.6 mmol) in acetonitrile (75 mL) according to the general procedure. The crude product was purified by recrystallisation (CH_2Cl_2

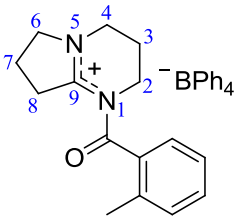
/ hexane), yielding the title compound (7.62 g, 93%) as a white solid. mp: 117-119 °C; ^{1}H NMR (300 MHz; CD_3CN): δ_H = 7.71 (3H, app. d, *J* = 8.7 Hz, Ph-*H*), 7.57 (2H, app. t, *J* = 7.7 Hz, Ph-*H*), 7.35-7.27 (8H, br. s, BPh_4-*H*), 7.02 (8H, app. t, *J* = 7.4 Hz, BPh_4-*H*), 6.87 (4H, app. t, *J* = 7.1 Hz, BPh_4-*H*), 3.75 (2H, app. t, *J* = 7.6 Hz, H^6), 3.65 (2H, app. t, *J* = 5.5 Hz, H^2), 3.40 (2H, app. t, *J* = 5.8 Hz, H^4), 3.19 (2H, app. t, *J* = 7.7 Hz, H^8), 2.17-1.93 (4H, m, H^3 and H^7); ^{13}C{^{1}H} NMR (75 MHz, CD_3CN): δ_C = 171.63, 168.77, 165.72, 165.06, 164.41, 163.76, 136.70, 136.68, 134.58, 132.84, 130.05, 129.96, 126.64, 126.60, 126.57, 126.53, 122.77, 56.11, 46.88, 45.37, 35.18, 19.87, 19.50; IR (film, cm^{-1}): ν_{max} = 1714 (C=O), 1635, 1487; HRMS: *m*/*z* (ES) 229.1416, $C_{14}H_{17}N_2O$ $[M]^+$ requires 229.1336.

_N_-Acetyl DBN BPh_4 (360)



DBN (**6**) (1.19 mL, 10 mmol) was added dropwise to a solution of sodium tetraphenylborate (3.42 g, 10 mmol) and acetyl chloride (**367**) (0.74 mL, 10.4 mmol) in acetonitrile (50 mL) according to the general procedure. The crude product was purified by recrystallisation (CH_2Cl_2 / hexane), yielding the title compound (4.72 g, 97%) as transparent crystalline plates. mp: 185 °C (dec.); ^{1}H NMR (300 MHz; CD_2Cl_2): δ_H = 7.41-7.34 (8H, br. s, BPh_4-*H*), 7.02 (8H, app. t, *J* = 7.4 Hz, BPh_4-*H*), 6.86 (4H, app. t, *J* = 7.2 Hz, BPh_4-*H*), 3.23 (2H, app. t, *J* = 8.1 Hz, H^6), 3.12 (2H, app. t, *J* = 7.8 Hz, H^2), 2.70 (2H, app. t, *J* = 5.8 Hz, H^4), 2.49 (2H, app. t, *J* = 5.9 Hz, H^8), 2.02 (3H, s, $COCH_3$), 1.87 (2H, app. p, *J* = 8.0 Hz, H^7), 1.34 (2H, app. p, *J* = 6.0 Hz, H^3), ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): δ_C = 170.89, 166.37, 165.18, 164.53, 163.88, 163.23, 136.16, 136.14, 126.15, 126.11, 126.07, 126.04, 122.22, 55.13, 43.93, 43.54, 35.53, 24.16, 18.57, 18.28; IR (film, cm^{-1}): ν_{max} = 1746 (C=O), 1640, 1479, 1428; HRMS: *m*/*z* (ES) 167.1277, $C_9H_{15}N_2O$ $[M]^+$ requires 167.1179.

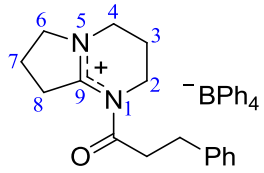
_N-o_-Toluoyl DBN BPh_4 (361)



DBN (**6**) (0.62 mL, 5 mmol) was added dropwise to a solution of sodium tetraphenylborate (1.71 g, 5 mmol) and *o*-toluoyl chloride (**216**) (0.68 mL, 5.2 mmol) in acetonitrile (25 mL)

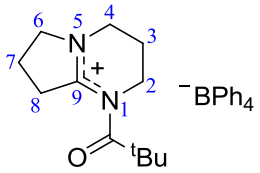
according to the general procedure. The crude product was purified by recrystallisation (CH_2Cl_2 / hexane), yielding the title compound (2.75 g, 98%) as white crystals. mp: 173-176 °C; ^{1}H NMR (300 MHz; CD_3CN): δ_H = 7.57-7.51 (1H, m, Tol-*H*), 7.44-7.35 (11H, m, 3 Tol-*H* and 8 BPh_4-*H*), 7.07 (8H, app. t, *J* = 7.4 Hz, BPh_4-*H*), 6.92 (4H, app. t, *J* = 7.2 Hz, BPh_4-*H*), 3.65 (2H, app. t, *J* = 7.7 Hz, H^6), 3.50 (2H, app. t, *J* = 5.6 Hz, H^2), 3.28 (2H, app. t, *J* = 6.0 Hz, H^4), 3.15 (2H, app. t, *J* = 7.9 Hz, H^8), 2.41 (3H, s, Tol-CH_3), 2.09-1.89 (4H, m, H^3 and H^7); ^{13}C{^{1}H} NMR (75 MHz, CD_3CN): δ_C = 171.57, 168.53, 165.75, 165.09, 164.44, 163.79, 137.87, 136.75, 136.73, 136.72, 136.70, 133.22, 132.93, 132.48, 128.16, 127.19, 126.66, 126.62, 126.59, 126.55, 122.80, 56.13, 45.65, 45.43, 35.71, 19.58, 19.54, 19.26; IR (film, cm^{-1}): ν_{max} = 1763 (C=O), 1653, 1478, 1427; HRMS: *m*/*z* (ES) 243.1628, $C_{15}H_{19}N_2O$ $[M]^+$ requires 243.1492.

_N_-Hydrocinnamoyl DBN BPh_4 (362)



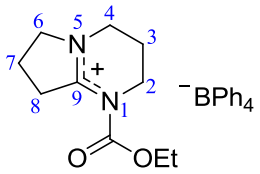
DBN (**6**) (1.19 mL, 10 mmol) was added dropwise to a solution of sodium tetraphenylborate (3.42 g, 10 mmol) and hydrocinnamoyl chloride (**226**) (1.55 mL, 10.4 mmol) in acetonitrile (50 mL) according to the general procedure. The crude product was purified by recrystallisation (CH_2Cl_2 / hexane), yielding the title compound (4.23 g, 73%) as white crystalline plates. mp: 167-170 °C; ^{1}H NMR (300 MHz; CD_2Cl_2): δ_H = 7.41-7.34 (8H, m, BPh_4-*H*), 7.33-7.21 (5 H, m, Ph-*H*), 7.01 (8H, app. t, *J* = 7.5 Hz, BPh_4-*H*), 6.86 (4H, app. t, *J* = 7.2 Hz, BPh_4-*H*), 3.29 (2H, app. t, *J* = 8.1 Hz, H^6), 3.19 (2H, app. t, *J* = 7.8 Hz, H^2), 2.93 (2H, app. t, *J* = 7.2 Hz, H^4), 2.70 (2H, app. t, *J* = 5.7 Hz, H^8), 2.58-2.53 (4H, m, CH_2H_2Ph), 1.93 (2H, app. p, *J* = 7.9 Hz, H^7), 1.36 (2H, app. p, *J* = 5.8 Hz, H^3); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): δ_C = 173.30, 166.89, 165.66, 165.01, 164.36, 163.71, 140.22, 136.61, 129.47, 129.29, 127.48, 126.57, 126.54, 126.50, 126.47, 122.65, 55.63, 44.43, 43.21, 38.11, 36.04, 30.69, 19.01, 18.79; IR (film, cm^{-1}): ν_{max} = 1742 (C=O), 1634, 1436, 1427; HRMS: *m*/*z* (ES) 257.1643, $C_{16}H_{21}N_2O$ $[M]^+$ requires 257.1654.

_N_-Pivaloyl DBN BPh_4 (363)



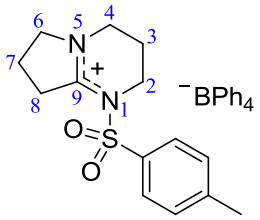
DBN (**6**) (0.62 mL, 5 mmol) was added dropwise to a solution of sodium tetraphenylborate (1.71 g, 5 mmol) and pivaloyl chloride (**230**) (0.64 mL, 5.2 mmol) in acetonitrile (25 mL) according to the general procedure. The crude product was purified by recrystallisation (CH_2Cl_2 / hexane), yielding the title compound (2.58 g, 98%) as white crystals. mp: 157-158 °C; ^{1}H NMR (300 MHz; CD_3CN): δ_H = 7.34-7.28 (8H, m, BPh_4-*H*), 7.02 (8H, app. t, *J* = 7.4 Hz, BPh_4-*H*), 6.87 (4H, app. t, *J* = 7.3 Hz, BPh_4-*H*), 3.75 (2H, app. t, *J* = 5.5 Hz, *H*^{2}), 3.60 (2H, app. t, *J* = 7.5 Hz, *H*^{6}), 3.25 (2H, app. t, *J* = 5.9 Hz, *H*^{4}), 3.11 (2H, app. t, *J* = 7.9 Hz, *H*^{8}), 2.07-1.90 4H, m, *H*^{3} and *H*^{7}), 1.34 (9H, s, $(CH_3)_3$); ^{13}C{^{1}H} NMR (75 MHz, CD_3CN): δ_C = 181.33, 168.24, 165.71, 165.06, 164.41, 163.76, 136.70, 136.68, 126.64, 126.61, 126.57, 126.54, 122.78, 118.31, 56.05, 45.33, 44.90, 42.98, 34.84, 28.08, 19.75, 19.26; IR (film, cm^{-1}): ν_{max} = 1718 (C=O), 1642, 1470, 1426; HRMS: *m*/*z* (ES) 209.1764, $C_{12}H_{21}N_2O$ $[M]^+$ requires 209.1649.

_N_-Ethyl carboxyl DBN BPh_4 (364)



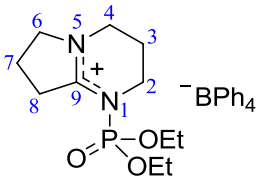
DBN (**6**) (0.62 mL, 5 mmol) was added dropwise to a solution of sodium tetraphenylborate (1.71 g, 5 mmol) and ethyl chloroformate (**371**) (0.64 mL, 5.2 mmol) in acetonitrile (25 mL) according to the general procedure. The crude product was purified by recrystallisation (CH_2Cl_2 / hexane), yielding the title compound (2.45 g, 95%) as a white powder. mp: 156-157 °C; ^{1}H NMR (300 MHz; CD_3CN): δ_H = 7.27 (8H, br. s, BPh_4-*H*), 6.99 (8H, app. t, *J* = 7.3 Hz, BPh_4-*H*), 6.83 (4H, app. t, *J* = 7.2 Hz, BPh_4-*H*), 4.30 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 3.77-3.67 (4H, br. m, *H*^{2} and *H*^{6}), 3.41-3.30 (4H, br. m, *H*^{4} and *H*^{8}), 2.12-1.90 (4H, m, *H*^{3} and *H*^{7}), 1.31 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, CD_3CN): δ_C = 168.66, 165.76, 165.11, 164.46, 163.80, 152.22, 136.76, 136.74, 136.73, 136.71, 126.65, 126.61, 126.57, 126.54, 122.78, 66.23, 56.54, 45.10, 44.02, 36.09, 19.09, 18.76, 14.26; IR (film, cm^{-1}): ν_{max} = 1763 (C=O), 1654, 1478; HRMS: *m*/*z* (ES) 197.1395, $C_{10}H_{17}N_2O_2$ $[M]^+$ requires 197.1285.

_N_-Sulfonyl DBN BPh_4 (365)



DBN (**6**) (0.62 mL, 5 mmol) was added dropwise to a solution of sodium tetraphenylborate (1.71 g, 5 mmol) and tosyl chloride (**372**) (0.99 g, 5.2 mmol) in acetonitrile (25 mL) according to the general procedure. The crude product was purified by recrystallisation (CH_2Cl_2 / hexane), yielding the title compound (1.99 g, 66%) as a beige powder. mp: 185 °C (dec.); ^{1}H NMR (300 MHz; CD_2Cl_2): δ_H = 7.72 (2H, d, *J* = 8.3 Hz, Tol-*H*), 7.46 (2H, d, *J* = 8.3 Hz, Tol-*H*), 7.34 (8H, br. s, BPh_4-*H*), 6.97 (8H, app. t, *J* = 7.4 Hz, BPh_4-*H*), 6.82 (4H, app. t, *J* = 7.2 Hz, BPh_4-*H*), 3.39 (2H, app. t, *J* = 5.7 Hz, H^4), 3.13 (2H, app. t, *J* = 8.0 Hz, H^6), 2.87 (2H, app. t, *J* = 7.7 Hz, H^8), 2.48 (3H, s, Tol-CH_3), 2.32 (2H, app. t, *J* = 5.7 Hz, H^2), 1.67 (2H, app. p, *J* = 7.9 Hz, H^7), 1.46-1.38 (2H, m, H^3); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): δ_C = 165.18, 165.00, 164.53, 163.88, 163.22, 148.71, 136.20, 136.18, 132.85, 131.53, 128.15, 126.11, 126.07, 126.04, 126.00, 122.21, 55.68, 44.72, 44.03, 33.98, 22.04, 18.82, 17.81; IR (film, cm^{-1}): ν_{max} = 1636, 1476, 1427; HRMS: *m*/*z* (ES) 279.1209, $C_{14}H_{19}N_2O_2S$ $[M]^+$ requires 279.1167.

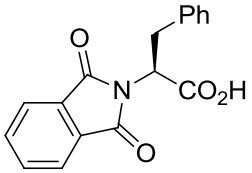
_N_-Phosphoryl DBN BPh_4 (366)



DBN (**6**) (0.62 mL, 5 mmol) was added dropwise to a solution of sodium tetraphenylborate (1.71 g, 5 mmol) and diethyl chlorophosphate (**373**) (0.75 mL, 5.2 mmol) in acetonitrile (25 mL) according to the general procedure. The crude product was purified by recrystallisation (CH_2Cl_2 / hexane), yielding the title compound (2.53 g, 87%) as a white powder. mp: 132-135 °C; ^{1}H NMR (300 MHz; CD_3CN): δ_H = 7.31-7.25 (8H, br. m, BPh_4-*H*), 7.00 (8H, app. t, *J* = 7.4 Hz, BPh_4-*H*), 6.84 (4H, app. t, *J* = 7.2 Hz, BPh_4-*H*), 4.26-4.07 (4H, m, (OCH_2CH$_3$)$_2$), 3.65 (2H, app. t, *J* = 7.6 Hz, H^6), 3.55-3.50 (2H, m, H^2), 3.31 (2H, app. t, *J* = 5.9 Hz, H^4), 3.19 (2H, app. t, *J* = 8.0 Hz, H^8), 2.10-1.90 (4H, m, H^3 and H^7), 1.33 (6H, app. td, *J* = 7.1 and 1.0 Hz, (OCH$_2$CH_3)$_2$); ^{13}C{^{1}H} NMR (75 MHz, CD_3CN): δ_C = 165.72, 165.07, 164.41, 163.76, 136.72, 136.70, 136.68, 136.67, 126.63, 126.60, 126.56, 126.52, 122.76, 66.21, 66.14, 56.40, 44.79, 44.64, 34.79, 19.25, 19.20, 18.61, 16.34, 16.25; ^{31}P{^{1}H} NMR (121 MHz, CD_3CN): δ_p = –1.70;

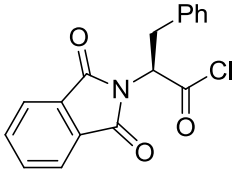
IR (film, cm^{-1}): ν_{max} = 1644 (C=O), 1478; HRMS: *m*/*z* (ES) 261.1455, $C_{11}H_{22}N_2O_3P$ $[M]^+$ requires 261.1363.

_N_-Phthaloyl-L-phenylalanine (376)



L-Phenylalanine (**374**) (4.96 g, 30 mmol) and phthalic anhydride (**375**) (4.44 g, 30 mmol) were added to a 100 mL round-bottom flask. Toluene (45 mL) and triethylamine (0.42 mL, 3 mmol) were added and a Dean-Stark trap was fitted. The resulting solution was heated at reflux for 16 hours before being cooled to room temperature and concentrated under reduced pressure to give a cream solid. The solid was suspended in H_2O (60 mL) and 1M HCl (5 mL) before being collected *via* Büchner filtration. The crude was purified by recrystallisation from hot ethanol (20 mL) and water (15 mL) to give the title compound (8.24 g, 93%) as colourless needles. $[\alpha]_D^{17}$ = -194 (*c* = 0.85 g/100 mL in $CHCl_3$); ^1H NMR (300 MHz; $CDCl_3$): δ_H = 8.61 (1H, br. s, O*H*), 7.71-7.67 (2H, m, Ar-*H*), 7.62-7.58 (2H, m, Ar-*H*), 7.14-7.02 (5H, m, Ph-*H*), 5.15 (1H, app. t, *J* = 8.3 Hz, NC*H*), 3.52 (2H, app. d, *J* = 8.6 Hz, CH_2Ph); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 174.59, 167.53, 136.54, 134.30, 131.60, 128.94, 128.73, 127.07, 123.68, 53.18, 34.51; HRMS: *m*/*z* (ES) 294.0777, $C_{17}H_{12}NO_4$ $[M+H]^+$ requires 294.0766.

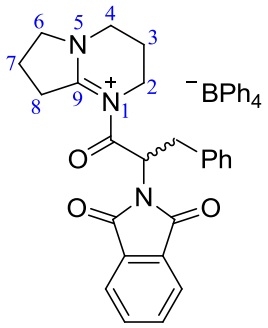
(*S*)-2-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropanoyl chloride (377)



N-Phthaloyl-L-phenylalanine (**376**) (1.49 g, 5 mmol) was added to a 100 mL round-bottom flask and purged with nitrogen. Dry dichloromethane (15 mL) and a drop of DMF were added and the solution was cooled to 0 °C. Oxalyl chloride (1.28 mL, 15 mmol) was added dropwise and the resulting solution was stirred at 0 °C for ten minutes before warming to room temperature and stirring for one hour. The solution was concentrated under reduced pressure to give a pale yellow solid. The crude was recyrstallised from CH_2Cl_2 / hexane and the title compound (1.19 g, 76%) was isolated as a cream solid. ^1H NMR (300 MHz; $CDCl_3$): δ_H = 7.79-7.73 (2H, m, Ar-*H*), 7.69-7.64 (2H, m, Ar-*H*), 7.16-7.06 (5H, m, Ph-*H*), 5.25 (1H, dd, *J* = 10.8, 5.3 Hz, NC*H*CH^AH^B), 3.59 (1H, dd, *J* = 14.2, 5.3 Hz, NCHC*H*$^AH^B$), 3.48 (1H, dd, *J* = 14.2, 10.8 Hz,

NCHCH^{A}*H*^{B}); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.27, 166.85, 135.46, 134.70, 131.42, 129.00, 128.91, 127.47, 124.02, 61.62, 34.91.

_N_-Phth-Phe-DBN·BPh$_4$ (380)



In a modified procedure, sodium tetraphenylborate (1.29 g, 3.8 mmol) and PhthN-Phe-Cl (**377**) (1.23 g, 3.9 mmol) were added to a round bottom flask and placed under a nitrogen atmosphere. Dry acetonitrile (40 mL) was added and the resulting solution cooled to -8 °C using a salt-ice bath. DBN (**6**) (0.47 mL, 3.8 mmol), diluted in acetonitrile (10 mL) and cooled to 0 °C, was added dropwise over a period of ten minutes and the resulting solution was stirred at -8 °C for one hour. The reaction mixture was then filtered through a pad of Celite®, washing thoroughly with acetonitrile, to remove the sodium chloride precipitate. The filtrated was concentrated under reduced pressure to yield the title compound (2.28 g, 83%) as a yellow powder. mp: 97-99 °C; $[\alpha]_D^{17}$ = -11.2 (*c* = 1.25 g/100 mL in MeCN); ^{1}H NMR (500 MHz; $CDCl_3$): δ_H = 7.85-7.82 (4H, m, Phth-*H*), 7.38-7.34 (8H, br. s, BPh$_4$-*H*), 7.23-7.18 (5H, m, Ph-*H*), 7.06 (8H, app. t, *J* = 7.4 Hz, BPh$_4$-*H*), 6.91 (4H, app. t, *J* = 7.2 Hz, BPh$_4$-*H*), 5.55 (1H, dd, *J* = 10.1, 5.0 Hz, NC*H*CH^{A}H^{B}), 3.84-3.79 (1H, m, *H*^{2A}), 3.76-3.68 (1H, m, *H*^{2B}), 3.66-3.57 (2H, m, *H*^{6}), 3.53-3.49 (1H, m, NCHC*H*^{A}H^{B}), 3.33 (1H, dd, *J* = 14.1, 10.3 Hz, NCHCH^{A}*H*^{B}), 3.26-3.18 (2H, m, *H*^{4}), 3.14-3.06 (2H, m, *H*^{8}), 2.20-2.11 (2H, m, *H*^{7}), 1.92-1.85 (2H, m, *H*^{3}); ^{13}C{^{1}H} NMR (75 MHz, CD_2Cl_2): δ_C = 171.50, 168.46, 167.84, 165.36, 164.97, 164.58, 164.19, 137.01, 136.72, 136.71, 136.08, 132.02, 130.38, 129.48, 128.06, 126.63, 126.61, 126.59, 126.57, 124.65, 122.79, 56.16, 54.06, 45.00, 43.99, 35.49, 34.77, 19.61, 19.03; IR (film, cm^{-1}): ν_{max} = 1716 (C=O), 1643, 1579, 1477; HRMS: *m/z* (ES) 402.1789, $C_{24}H_{24}N_3O_3$ $[M]^+$ requires 402.1818.

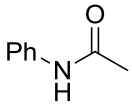
5.3.3 General Procedure for the *N*-Acylation of Amines with *N*-Acyl DBN·BPh$_4$ Salts

The appropriate *N*-acyl-DBN·BPh$_4$ (1.3 equiv., 0.65 mmol) is added to a Radleys carousel tube (150 × 24 mm fitted with gas-tight threaded PTFE caps with a suba-seal, sidearm and inlet valve) and purged with nitrogen. Dry acetonitrile (2 mL) and the appropriate amine (1 equiv., 0.5 mmol) are added and the resulting solution is heated at 80 °C for one hour before being

cooled to room temperature. The reaction mixture is filtered before being concentrated under reduced pressure. The crude product is suspended in the minimum amount of hot ethyl acetate and allow to cool before the mixture is filtered to remove the remaining *N*-acyl-DBN salt and DBN·HBPh$_4$. If necessary, the amide can be further purified by dissolving in ethyl acetate and washing successively with 1M HCl, 1M NaOH, and brine before being dried over MgSO$_4$, filtered and concentrated under reduced pressure.

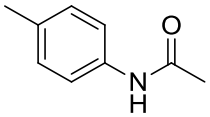
5.3.4 Secondary Amide Compound Data

_N_-Phenylacetamide (389)[258]



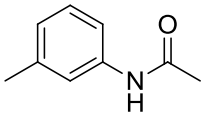
Aniline (**381**) (0.05 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh$_4$ (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for twenty-four hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.061 g, 90%) as a brown solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.89 (1H, br. s, N*H*), 7.42 (2H, d, *J* = 7.9 Hz, Ph-*H*), 7.21 (2H, t, *J* = 7.6 Hz, Ph-*H*), 7.01 (1H, t, *J* = 7.4 Hz, Ph-*H*), 2.06 (3H, s, C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.09, 138.03, 129.01, 124.44, 120.25, 24.49; HRMS: *m*/*z* (ES) 136.0765, $C_8H_{10}NO$ $[M+H]^+$ requires 136.0762.

_N_-(_p_-Tolyl)acetamide (390)[258]



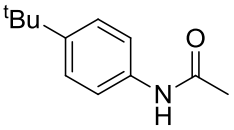
p-Toluidine (**382**) (0.054 g, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh$_4$ (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for twenty-four hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.070 g, 94%) as a beige solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 8.01 (1H, br. s, N*H*), 7.38 (2H, d, *J* = 8.3 Hz, Tol-*H*), 7.08 (2H, d, *J* = 8.2 Hz, Tol-*H*), 2.29 (3H, s, Tol-C*H*$_3$), 2.12 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 168.91, 135.55, 133.90, 129.44, 120.28, 24.43, 20.93; HRMS: *m*/*z* (ES) 172.0761, $C_9H_{11}NNaO$ $[M+Na]^+$ requires 172.0738.

_N_-(_m_-Tolyl)acetamide (391)[258]



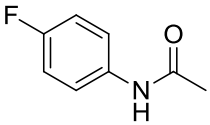
_m_-Toluidine (**383**) (0.054 mL, 0.5 mmol) was added to a solution of _N_-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for twenty-four hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.074 g, 99%) as a beige solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 8.11 (1H, br. s, N*H*), 7.28 (1H, s, Tol-*H*), 7.21 (1H, t, *J* = 8.3 Hz, Tol-*H*), 7.07 (1H, t, *J* = 7.7 Hz, Tol-*H*), 6.81 (1H, d, *J* = 7.5 Hz, Tol-*H*), 2.20 (3H, s, Tol-C*H*$_3$), 2.04 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.11, 138.80, 138.06, 128.73, 125.09, 120.86, 117.29, 24.46, 21.49; HRMS: *m*/*z* (ES) 150.0979, $C_9H_{12}NO$ $[M+H]^+$ requires 150.0914.

_N_-(4-(_tert_-Butyl)phenyl)acetamide (392)[259]



4-_t_-Butylaniline (**385**) (0.080 mL, 0.5 mmol) was added to a solution of _N_-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for twenty-four hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.078 g, 82%) as a beige solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.81 (1H, br. s, N*H*), 7.43 (2H, d, *J* = 8.5 Hz, Ar-*H*), 7.31 (2H, d, *J* = 8.6 Hz, Ar-*H*), 2.14 (3H, s, COC*H*$_3$), 1.29 (9H, s, (C*H*$_3$)$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 168.79, 147.29, 135.44, 125.82, 120.01, 34.44, 31.45, 24.51; HRMS: *m*/*z* (ES) 192.1403, $C_{12}H_{18}NO$ $[M+H]^+$ requires 192.1388.

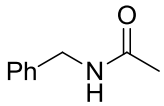
_N_-(4-Fluorophenyl)acetamide (393)[258]



4-Fluoroaniline (**386**) (0.048 mL, 0.5 mmol) was added to a solution of _N_-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for twenty-four hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.058 g, 76%) as a beige solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.89 (1H, br. s, N*H*), 7.46-7.41 (2H, m, Ar-*H*), 6.97 (2H, t, *J* = 8.6 Hz, Ar-*H*), 2.13 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 168.83, 159.48 (d,

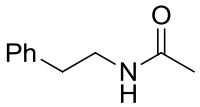
J = 242.6 Hz, F*C*), 134.06 (d, *J* = 2.9 Hz, FCCHCH*C*), 122.06 (d, *J* = 7.9 Hz, FCCH*C*H), 115.65 (d, *J* = 22.5 Hz, FC*C*H), 24.38; HRMS: *m*/*z* (ES) 154.0685, C_8H_9FNO $[M+H]^+$ requires 154.0668.

_N_-Benzylacetamide (403)[260]



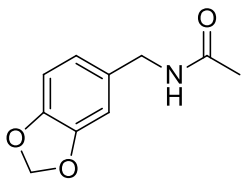
Benzylamine (**395**) (0.055 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.074 g, 99%) as a brown solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.26-7.16 (5H, m, Ph-*H*), 6.08 (1H, br. s, N*H*), 4.30 (2H, d, *J* = 5.8 Hz, CH_2N), 1.89 (3H, s, COCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.17, 138.36, 128.73, 127.85, 127.52, 43.73, 23.23; HRMS: *m*/*z* (ES) 172.0755, $C_9H_{11}NNaO$ $[M+Na]^+$ requires 172.0738.

_N_-Phenethylacetamide (404)[183]



2-Phenethylamine (**396**) (0.063 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with brine before being dried over $MgSO_4$ and concentrated to give the title compound (0.079 g, 97%) as a brown oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.26-7.09 (5H, m, Ph-*H*), 5.47 (1H, br. s, N*H*), 3.39 (2H, q, *J* = 6.9 Hz, NHC$H_2$$H_2$Ph), 2.71 (2H, t, *J* = 7.0 Hz, NHC$H_2$$H_2$Ph), 1.81 (3H, s, COC$H_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.31, 138.95, 128.82, 128.74, 126.62, 40.78, 35.67, 23.39; HRMS: *m*/*z* (ES) 186.0934, $C_{10}H_{13}NNaO$ $[M+Na]^+$ requires 186.0889.

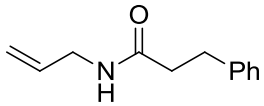
_N_-(Benzo[*d*][1,3]dioxol-5-ylmethyl)acetamide (405)[261]



Piperonylamine (**397**) (0.062 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to

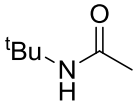
the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.068 g, 70%) as a light brown solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 6.69-6.62 (3H, m, Ar-*H*), 6.00 (1H, br. s, N*H*), 5.85 (2H, s, OCH_2O), 4.23 (2H, d, *J* = 5.6 Hz, CH_2N), 1.92 (3H, s, COCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.10, 147.98, 147.04, 132.25, 121.18, 108.52, 108.36, 101.15, 43.61, 23.30; HRMS: *m*/*z* (ES) 194.0814, $C_{10}H_{12}NO_3$ $[M+H]^+$ requires 194.0817.

_N_-Allyl-3-phenylpropanamide (411)[262]



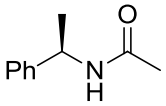
Allylamine (**399**) (0.038 mL, 0.5 mmol) was added to a solution of *N*-hydrocinnamoyl DBN·BPh_4 (**362**) (0.375 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.093 g, 98%) as a white solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.20-7.16 (2H, m, Ph*H*), 7.11-7.08 (3H, m, Ph*H*), 5.86 (1H, br. s, N*H*), 5.72-5.59 (1H, m, H_2CC*H*), 4.99-4.94 (2H, m, H_2CCH), 3.72 (2H, t, *J* = 5.6 Hz, CH_2NH), 2.86 (2H, t, *J* = 7.7 Hz, CH_2Ph), 2.39 (2H, t, *J* = 7.6 Hz, CH_2CH$_2$Ph); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 172.24, 140.83, 134.15, 128.52, 128.34, 126.24, 116.19, 41.89, 38.31, 31.74; HRMS: *m*/*z* (ES) 212.1135, $C_{12}H_{15}NNaO$ $[M+Na]^+$ requires 212.1051.

_N_-(*tert*-Butyl)acetamide (408)[263]



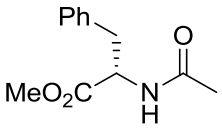
t-Butylamine (**400**) (0.053 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.044 g, 76%) as a brown solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 5.44 (1H, br. s, N*H*), 1.88 (3H, s, COCH_3), 1.31 (9H, s, (CH_3)$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.67, 51.22, 28.84, 24.61; HRMS: *m*/*z* (ES) 116.1091, $C_6H_{14}NO$ $[M+H]^+$ requires 116.1075.

(*R*)-*N*-(1-Phenylethyl)acetamide (409)[212]



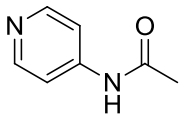
(*R*)-α-Methyl benzylamine (**401**) (0.064 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.054 g, 66%) as a brown solid. $[\alpha]_D^{22}$ = +121 (*c* = 0.97 g/100 mL in $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.28-7.19 (5H, m, Ph-*H*), 5.84 (1H, br. s, N*H*), 5.03 (1H, p, *J* = 7.2 Hz, C*H*CH_3), 1.88 (3H, s, COC*H*$_3$), 1.39 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.27, 143.31, 128.76, 127.45, 126.29, 48.91, 23.52, 21.84; HRMS: *m*/*z* (ES) 186.0922, $C_{10}H_{13}NNaO$ $[M+Na]^+$ requires 186.0895.

(*S*)-Methyl 2-acetamido-3-phenylpropanoate (410)[213]



L-Phenylalanine methyl ester (**402**) (0.090 g, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.110 g, 99%) as a beige solid. $[\alpha]_D^{18}$ = +84 (*c* = 0.68 g/100 mL in $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.24-7.16 (3H, m, Ph-*H*), 7.02 (2H, app. d, *J* = 7.1 Hz, Ph-*H*), 6.04 (1H, br. d, *J* = 7.3 Hz, N*H*), 4.80 (1H, dd, *J* = 13.6, 5.9 Hz, C*H*CH_AH_B), 3.64 (3H, s, OC*H*$_3$), 3.07 (1H, dd, *J* = 13.9, 5.9 Hz, CHC*H*$_A$H$_B$), 2.99 (1H, dd, *J* = 13.9, 5.9 Hz, $CHCH_AH_B$), 1.90 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 172.22, 169.81, 135.93, 129.28, 128.63, 127.18, 53.22, 52.38, 37.88, 23.14; HRMS: *m*/*z* (ES) 222.1132, $C_{12}H_{16}NO_3$ $[M+H]^+$ requires 222.1130.

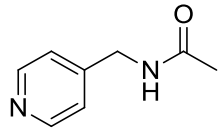
***N*-(Pyridin-4-yl)acetamide (420)**[264]



4-Aminopyridine (**416**) (0.047 g, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts

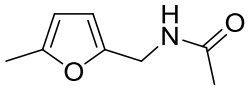
were filtered off to give the title compound (0.055 g, 81%) as a light brown solid; ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 9.72 (1H, br. s, N*H*), 8.42 (2H, d, *J* = 6.3 Hz, py-CHC*H*N), 7.58 (2H, dd, *J* = 5.1, 1.3 Hz, py-C*H*CHN), 2.18 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.15, 150.06, 146.30, 113.98, 24.68; HRMS: *m*/*z* (ES) 137.0817, $C_7H_9N_2O$ $[M+H]^+$ requires 137.0710.

_N_-(Pyridin-4-ylmethyl)acetamide (421)[265]



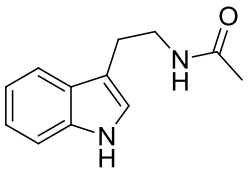
4-Picolylamine (**417**) (0.050 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.059 g, 78%) as a yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 8.45 (2H, d, *J* = 6.1 Hz, py-CHC*H*N), 7.13 (2H, d, *J* = 5.9 Hz, py-C*H*CHN), 6.83 (1H, br. d, *J* = 7.0 Hz, N*H*), 4.35 (2H, d, *J* = 6.1 Hz, C*H*$_2$NH), 1.99 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.64, 149.81, 147.85, 122.36, 42.36, 23.09; HRMS: *m*/*z* (ES) 173.0709, $C_8H_{10}N_2NaO$ $[M+Na]^+$ requires 173.0691.

_N_-((5-Methylfuran-2-yl)methyl)acetamide (422)



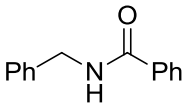
5-Methyl furfurylamine (**418**) (0.056 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.074 g, 97%) as an orange oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 6.14 (1H, br. s, N*H*), 6.00 (1H, d, *J* = 2.9 Hz, OCC*H*), 5.80 (1H, d, *J* = 2.1 Hz, OCC*H*), 4.26 (2H, d, *J* = 5.4 Hz, C*H*$_2$N), 2.17 (3H, s, CHCC*H*$_3$), 1.90 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.04, 151.89, 149.44, 108.32, 106.30, 36.72, 23.13, 13.53; HRMS: *m*/*z* (ES) 154.0885, $C_8H_{12}NO_2$ $[M+H]^+$ requires 154.0868.

***N*-(2-(1*H*-Indol-3-yl)ethyl)acetamide (423)**[266]



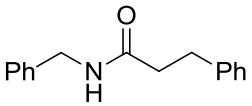
Tryptamine (**419**) (0.080 g, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.042 g, 42%) as a brown oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 8.29 (1H, br. s, CCHN*H*), 7.51 (1H d, *J* = 7.8 Hz, Ar-*H*), 7.30-7.27 (1H, m, Ar-*H*), 7.14-7.01 (2H, m, Ar-*H*), 6.92 (1H, s, CC*H*NH), 5.55 (1H, br. s, CON*H*), 3.50 (2H, q, *J* = 6.4 Hz, CH_2NH), 2.88 (2H, t, *J* = 6.7 Hz, CH_2CH_2NH), 1.83 (3H, s, COCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.33, 136.56, 128.45, 127.45, 122.24, 119.52, 118.75, 112.93, 111.46, 39.98, 25.37, 23.47; HRMS: *m*/*z* (ES) 225.1038, $C_{12}H_{14}N_2NaO$ $[M+Na]^+$ requires 225.1004.

***N*-Benzyl benzamide (424)**[260]



Benzylamine (**395**) (0.055 mL, 0.5 mmol) was added to a solution of *N*-benzoyl DBN·BPh_4 (**275**) (0.356 g, 0.65 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.077 g, 78%) as a beige solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.73-7.70 (2H, m, Ph*H*), 7.43-7.18 (8H, m, Ph*H*), 6.36 (1H, br. s, N*H*), 4.58 (2H, d, *J* = 5.7 Hz, CH_2N); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 167.35, 138.21, 134.43, 131.56, 128.82, 128.62, 127.95, 126.66, 126.97, 44.17; HRMS: *m*/*z* (ES) 212.1067 , $C_{14}H_{14}NO$ $[M+H]^+$ requires 212.1075.

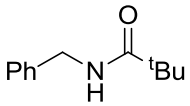
***N*-Benzyl-3-phenylpropanamide (425)**[260]



Benzylamine (**395**) (0.055 mL, 0.5 mmol) was added to a solution of *N*-hydrocinnamoyl DBN·BPh_4 (**362**) (0.375 g, 0.65 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with 1M HCl, 1M NaOH, and brine before being dried over $MgSO_4$, filtered, and concentrated to

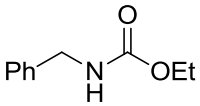
give the title compound (0.087 g, 73%) as a white solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.23-7.03 (10H, m, Ph-*H*), 5.78 (1H, br. s, N*H*), 4.28 (2H, d, *J* = 5.7 Hz, HNC*H*$_2$Ph), 2.89 (2H, t, *J* = 7.6 Hz, $COCH_2CH_2Ph$), 2.41 (2H, t, *J* = 7.6 Hz, $COCH_2CH_2Ph$); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 172.05, 140.87, 138.27, 128.71, 128.62, 128.48, 127.78, 127.49, 126.32, 43.61, 38.50, 31.80; HRMS: *m*/*z* (ES) 240.1375, $C_{16}H_{18}NO$ $[M+H]^+$ requires 240.1388.

_N_-Benzylpivalamide (426)[267]



Benzylamine (**395**) (0.055 mL, 0.5 mmol) was added to a solution of *N*-pivaloyl DBN·BPh_4 (**363**) (0.343 g, 0.65 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with 1M HCl, 1M NaOH, and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.094 g, 98%) as a pale yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.27-7.15 (5H, m, Ph-*H*), 6.01 (1H, br. s, N*H*), 4.34 (2H, d, *J* = 5.6 Hz, HNC*H*$_2$Ph), 1.14 (9H, s, $C(CH_3)_3$); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 178.43, 138.72, 128.71, 127.61, 127.40, 43.55, 38.74, 27.65; HRMS: *m*/*z* (ES) 214.1331, $C_{12}H_{17}NNaO$ $[M+Na]^+$ requires 214.1203.

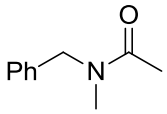
Ethyl benzylcarbamate (427)[268]



Benzylamine (**395**) (0.055 mL, 0.5 mmol) was added to a solution of *N*-ethyl carboxyl DBN·BPh_4 (**364**) (0.336 g, 0.65 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with 1M HCl, 1M NaOH, and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.073 g, 82%) as a pale yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.45-7.20 (5H, m, Ph-*H*), 5.95 (1H, br. s, N*H*), 4.29 (2H, d, *J* = 5.9 Hz, NC*H*$_2$Ph), 4.08 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 1.18 (3H, t, *J* = 7.1 Hz, OCH_2CH_3); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$): δ_C = 157.22, 134.86, 128.80, 128.06, 127.61, 61.19, 45.18, 14.77.

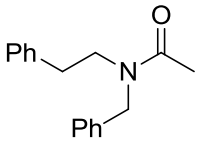
5.3.5 Tertiary Amide Compound Data

_N_-Benzyl-_N_-methylacetamide (436)[183]



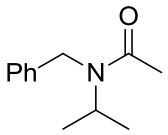
_N_-Benzyl-_N_-methylamine (**428**) (0.065 mL, 0.5 mmol) was added to a solution of _N_-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.081 g, 99%) as a dark brown oil. The product was analysed as a 4:3 mixture of rotamers (25 °C). *major* ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.31-7.08 (5H, m, Ph-*H*), 4.50 (2H, s, NC*H*$_2$Ph), 2.83 (3H, s, NC*H*$_3$), 2.07 (3H, s, COC*H*$_3$); *minor* ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.31-7.08 (5H, m, Ph-*H*), 4.44 (2H, s, NC*H*$_2$Ph), 2.86 (3H, s, NC*H*$_3$), 2.07 (3H, s, COC*H*$_3$); *major and minor* ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.07, 170.76, 137.32, 136.52, 128.94, 128.58, 127.98, 127.63, 127.33, 126.29, 54.22, 50.55, 35.54, 33.72, 21.86, 21.47; HRMS: *m*/*z* (ES) 186.0921, $C_{10}H_{13}NNaO$ $[M+Na]^+$ requires 186.0894.

_N_-Benzyl-_N_-phenethylacetamide (437)[269]



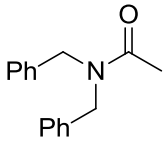
_N_-Benzyl-_N_-phenethylamine (**429**) (0.10 mL, 0.5 mmol) was added to a solution of _N_-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.124 g, 98%) as a dark brown oil. The product was analysed as a 1:1 mixture of rotamers (25 °C). ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.28-7.02 (20H, m, 4 Ph-*H*), 4.53 (2H, s, NC*H*$_2$Ph), 4.27 (2H, s, NC*H*$_2$Ph), 3.49 (2H, t, *J* = 7.5 Hz, NC*H*$_2$CH$_2$Ph), 3.34 (2H, t, *J* = 7.5 Hz, NC*H*$_2$CH$_2$Ph), 2.80-2.69 (4H, m, 2 NCH$_2$C*H*$_2$Ph), 2.04 (3H, s, COC*H*$_3$), 1.93 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.04, 170.78, 139.30, 138.24, 137.65, 136.84, 128.96, 128.89, 128.83, 128.78, 128.66, 128.55, 128.18, 127.65, 127.45, 126.83, 126.38, 126.36, 52.74, 49.50, 48.26, 48.13, 34.91, 34.03, 21.93, 21.32; HRMS: *m*/*z* (ES) 254.1640, $C_{17}H_{20}NO$ $[M+H]^+$ requires 254.1540.

_N_-Benzyl-_N_-isopropylacetamide (438)



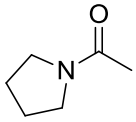
N-Benzyl-*N*-isopropylamine (**430**) (0.080 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with 1M HCl, 1M NaOH, and brine before being dried over $MgSO_4$ and concentrated to give the title compound (0.053 g, 55%) as a pale yellow oil. The product was analysed as a 4:3 mixture of rotamers (25 °C). *major* ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.29-7.10 (5H, m, Ph-*H*), 4.79 (1H, h, *J* = 6.8 Hz, C*H*$(CH_3)_2$), 4.38 (2H, s, CH_2Ph), 1.93 (3H, s, COCH_3), 1.01 (6H, d, *J* = 6.8 Hz, CH(CH_3)$_2$); *minor* ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.29-7.10 (5H, m, Ph-*H*), 4.46 (2H, s, CH_2Ph), 4.04 (1H, h, *J* = 6.7 Hz, C*H*$(CH_3)_2$), 2.15 (3H, s, COCH_3), 1.06 (6H, d, *J* = 6.7 Hz, CH(CH_3)$_2$); *major and minor* ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.51, 170.70, 139.68, 138.55, 128.77, 128.32, 127.16, 127.01, 126.60, 125.84, 49.84, 46.95, 45.54, 43.72, 22.66, 22.06, 21.51, 20.36; HRMS: *m*/*z* (ES) 214.1341, $C_{12}H_{17}NNaO$ $[M+Na]^+$ requires 214.1203.

_N,N_-Dibenzylacetamide (439)[270]



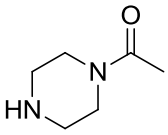
Dibenzylamine (**431**) (0.10 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.084 g, 70%) as a pale yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.32-7.06 (10H, m, Ph*H*), 4.51 (2H, s, NCH_2Ph), 4.35 (2H, s, NCH_2Ph), 2.13 (3H, s, COCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.26, 137.32, 136.41, 129.04, 128.67, 128.53, 128.45, 128.33, 127.72, 127.49, 126.44, 50.79, 48.01, 21.76; HRMS: *m*/*z* (ES) 262.1213, $C_{16}H_{17}NNaO$ $[M+Na]^+$ requires 262.1208.

1-(Pyrrolidin-1-yl)ethanone (440)[271]



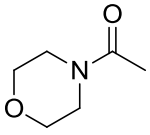
Pyrrolidine (**432**) (0.083 g, 1.0 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.243 g, 0.5 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.05 g, 88%) as a yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 3.34 (4H, app. q, *J* = 6.7 Hz, C*H*$_2$NC*H*$_2$), 1.95 (3H, s, COC*H*$_3$), 1.90-1.75 (4H, m, NCH$_2$C*H*$_2$C*H*$_2$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.40, 47.50, 45.63, 26.16, 24.65, 22.55; HRMS: *m*/*z* (ES) 136.0846 $C_6H_{11}NNaO$ $[M+Na]^+$ requires 136.0733.

1-(Piperazin-1-yl)ethanone (441)[272]



Piperazine (**433**) (0.043 g, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.243 g, 0.5 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.063 g, 99%) as a orange oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 3.55-3.51 (2H, m, C*H*$_2$NCOCH$_3$), 3.40-3.37 (2H, m, C*H*$_2$NCOCH$_3$), 2.83-2.76 (4H, m, C*H*$_2$NHC*H*$_2$), 2.12 (1H, br. s, N*H*), 2.04 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.11, 47.51, 46.28, 45.81, 42.51, 21.38; HRMS: *m*/*z* (ES) 151.0868, $C_6H_{12}N_2NaO$ $[M+Na]^+$ requires 151.0847.

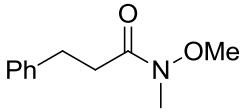
1-Morpholinoethanone (442)[237]



Morpholine (**434**) (0.044 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off to give the title compound (0.063 g, 97%) as a brown oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 3.65-3.60 (4H, m, C*H*$_2$OC*H*$_2$), 3.57-3.54 (2H, m, C*H*$_2$NCOCH$_3$), 3.41 (2H, t, *J* = 4.8 Hz, C*H*$_2$NCOCH$_3$), 2.05 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.19,

66.85, 66.60, 46.67, 41.76, 21.20; HRMS: *m/z* (ES) 152.0692, $C_6H_{11}NNaO_2$ $[M+Na]^+$ requires 152.0687.

_N_-Methoxy-_N_-methyl-3-phenylpropanamide (443)[273]



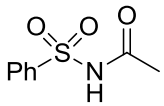
N,*O*-Dimethylhydroxylamine hydrochloride (**435**) (0.049 g, 0.5 mmol) was added to a solution of *N*-hydrocinnamoyl DBN·BPh_4 (**362**) (0.375 g, 0.65 mmol) and DBN (**6**) (0.070 mL, 0.6 mmol) in acetonitrile (2 mL) and heated at 80 °C for one hour according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with 1M HCl, 1M NaOH, and brine before being dried over $MgSO_4$ and concentrated to give the title compound (0.077 g, 80%) as a pale orange oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.25-7.10 (5H, m, Ph-*H*), 3.53 (3H, s, OC*H*$_3$), 3.11 (3H, s, NC*H*$_3$), 2.89 (2H, t, *J* = 7.8 Hz, C*H*$_2$CH$_2$Ph), 2.67 (2H, t, *J* = 7.8 Hz, CH$_2$C*H*$_2$Ph); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 173.88 141.50, 128.59, 128.58, 126.23, 61.34, 33.95, 30.83; HRMS: *m/z* (ES) 194.1209, $C_{11}H_{16}NO_2$ $[M+H]^+$ requires 194.1181.

5.3.6 General Procedure for the *N*-Acylation of Sulfonamides with *N*-Acetyl DBN·BPh_4

N-acetyl DBN·BPh_4 (**360**) (1.3 equiv., 0.65 mmol) and the appropriate sulfonamide (1 equiv., 0.5 mmol) are added to a Radleys carousel tube (150 × 24 mm fitted with gas-tight threaded PTFE caps with a suba-seal, sidearm and inlet valve) and purged with nitrogen. Dry acetonitrile (2 mL) and DBN (**6**) (20 mol%, 0.1 mmol) are added and the resulting solution is heated at 80 °C for 16 hours before being cooled to room temperature. The reaction mixture filtered before being concentrated under reduced pressure. The crude product is suspended in the minimum amount of hot ethyl acetate and allow to cool before the mixture is filtered to remove the remaining *N*-acetyl-DBN salt and DBN·$HBPh_4$. The filtrate is then washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

5.3.7 *N*-Acyl Sulfonamide Compound Data

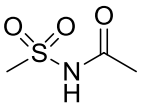
_N_-(Phenylsulfonyl)acetamide (452)[274]



DBN (**6**) (0.01 mL, 0.1 mmol) and acetonitrile (2 mL) were added to the *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and benzenesulfonamide (**444**) (0.079 g, 0.5 mmol) and the

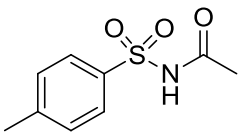
resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.083 g, 83%) as a light brown solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 9.05 (1H, br. s, N*H*), 7.99 (2H, d, *J* = 7.7 Hz, Ph-*H*), 7.59 (1H, t, *J* = 7.3 Hz, Ph-*H*), 7.49 (2H, t, *J* = 7.6 Hz, Ph-*H*), 2.00 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 168.51, 138.58, 134.21, 129.19, 128.38, 23.66; HRMS: *m*/*z* (ES) 200.0384, $C_8H_{10}NO_3S$ $[M+H]^+$ requires 200.0381.

_N_-(Methylsulfonyl)acetamide (453)



DBN (**6**) (0.01 mL, 0.1 mmol) and acetonitrile (2 mL) were added to the *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and methanesulfonamide (**445**) (0.048 g, 0.5 mmol) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.067 g, 98%) as a deep purple oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 6.00 (1H, br. s, N*H*), 3.23 (3H, s, SO_2CH_3), 2.13 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.40, 41.27, 24.05; HRMS: *m*/*z* (ES) 160.0029, $C_3H_7NNaO_3S$ $[M+Na]^+$ requires 160.0044.

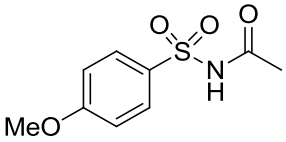
_N_-Tosylacetamide (454)[274]



DBN (**6**) (0.01 mL, 0.1 mmol) and acetonitrile (2 mL) were added to the *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and *p*-toluenesulfonamide (**446**) (0.086 g, 0.5 mmol) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.085 g, 80%) as a brown solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 9.15 (1H, br. s, N*H*), 7.86 (2H, d, *J* = 8.3 Hz, Tol-*H*), 7.27 (2H, d, *J* = 8.1 Hz, Tol-*H*), 2.37 (3H, s, Tol-C*H*$_3$), 1.99 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 168.69, 145.35,

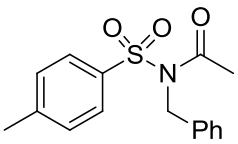
135.56, 129.79, 128.42, 23.62, 21.81; HRMS: *m*/*z* (ES) 214.0920, $C_9H_{12}NO_3S$ $[M+H]^+$ requires 214.0533.

_N_-((4-Methoxyphenyl)sulfonyl)acetamide (455)[274]



DBN (**6**) (0.01 mL, 0.1 mmol) and acetonitrile (2 mL) were added to the *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and 4-methoxybenzenesulfonamide (**447**) (0.094 g, 0.5 mmol) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.085 g, 74%) as a brown solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 9.01 (1H, br. s, N*H*), 7.92 (2H, d, *J* = 9.0 Hz, Ar-*H*), 6.93 (2H, d, *J* = 9.0 Hz, Ar-*H*), 3.81 (3H, s, OC*H*$_3$), 1.99 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 168.56, 164.12, 130.79, 129.85, 114.32, 55.86, 23.63; HRMS: *m*/*z* (ES) 230.0472, $C_9H_{12}NO_4S$ $[M+H]^+$ requires 230.0487.

_N_-Benzyl-_N_-tosylacetamide (458)[275]



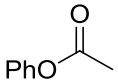
DBN (**6**) (0.01 mL, 0.1 mmol) and acetonitrile (2 mL) were added to the *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and *N*-benzyl-*p*-toluenesulfonamide (**450**) (0.131 g, 0.5 mmol) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in ethyl acetate and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.099 g, 65%) as a beige solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.53 (2H, d, *J* = 8.4 Hz, Tol-*H*), 7.31-7.17 (7H, m, Ar-*H*), 5.00 (2H, s, NC*H*$_2$Ph), 2.34 (3H, s, Tol-C*H*$_3$), 2.20 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.50, 145.05, 136.76, 136.59, 129.86, 128.72, 128.05, 127.86, 49.63, 25.01, 21.72; HRMS: *m*/*z* (ES) 304.1012, $C_{16}H_{18}NO_3S$ $[M+H]^+$ requires 304.1007.

5.3.8 General Procedure for the *O*-Acylation of Alcohols with *N*-Acetyl DBN·BPh_4

N-acetyl DBN·BPh_4 (**360**) (1.3 equiv., 0.65 mmol) is added to a Radleys carousel tube (150 × 24 mm fitted with gas-tight threaded PTFE caps with a suba-seal, sidearm and inlet valve) and purged with nitrogen. Dry acetonitrile (2 mL), the appropriate alcohol (1 equiv., 0.5 mmol), and DBN (**6**) (20 mol%, 0.1 mmol) are added and the resulting solution is heated at 80 °C for 16 hours before being cooled to room temperature. The reaction mixture is filtered before being concentrated under reduced pressure. Chloroform is then added to dissolve the product, whilst excess *N*-acetyl-DBN salt and DBN·$HBPh_4$ are insoluble and can be filtered off. The resulting solution is washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

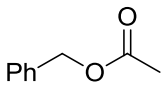
5.3.9 Ester Compound Data

Phenyl acetate (468)[276]



Phenol (**460**) (0.05 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in chloroform and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.057 g, 84%) as an orange oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.34-7.27 (2H, m, Ph-*H*), 7.18-7.12 (1H, m, Ph-*H*), 7.03-6.98 (2H, m, Ph-*H*), 2.22 (3H, s, COCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 169.65, 150.74, 129.52, 125.93, 121.66, 21.24; IR (film, cm^{-1}): ν_{max} = 1761 (C=O), 1679, 1593, 1493.

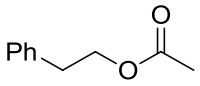
Benzyl acetate (469)[277]



Benzyl alcohol (**461**) (0.05 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and DBN (**6**) (0.01 mL, 0.1 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in chloroform and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.066 g, 88%) as a light brown oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.29-7.24 (5H, m, Ph-*H*), 5.03 (2H, s, OCH_2Ph), 2.02 (3H, s, COCH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$):

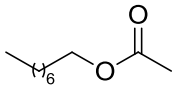
δ_C = 171.00, 136.01, 128.66, 128.36, 66.41, 21.11; IR (film, cm^{-1}): ν_{max} = 1735 (C=O), 1671, 1498, 1456.

Phenethyl acetate (470)[277]



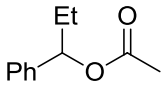
Phenethyl alcohol (**462**) (0.06 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and DBN (**6**) (0.01 mL, 0.1 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in chloroform and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.066 g, 80%) as a light brown oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.26-7.13 (5H, m, Ph-*H*), 4.21 (2H, t, *J* = 7.1 Hz, OC*H*$_2$$CH_2$Ph), 2.87 (2H, t, *J* = 7.1 Hz, OCH_2C*H*$_2$Ph), 1.96 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.17, 137.96, 129.02, 128.63, 126.70, 65.06, 35.23, 21.11; IR (film, cm^{-1}): ν_{max} = 1736 (C=O), 1671, 1498, 1455.

Octyl acetate (471)[278]



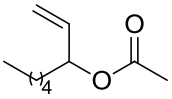
Octanol (**463**) (0.08 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and DBN (**6**) (0.01 mL, 0.1 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in chloroform and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.064 g, 74%) as a pale yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 3.98 (2H, t, *J* = 6.8 Hz, OC*H*$_2$$CH_2$), 1.97 (3H, s, COC*H*$_3$), 1.61-1.50 (2H, m, OCH_2C*H*$_2$), 1.31-1.18 (10H, m, (C*H*$_2$)$_5$$CH_3$), 0.81 (3H, t, *J* = 6.7 Hz, $(CH_2)_5$C*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.23, 64.70, 31.86, 29.29, 29.25, 28.69, 25.99, 22.70, 21.02, 14.12; IR (film, cm^{-1}): ν_{max} = 2927, 2857, 1740 (C=O).

(±)-1-Phenylpropyl acetate (472)[278]



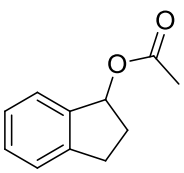
1-Phenyl-1-propanol (**464**) (0.07 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and DBN (**6**) (0.01 mL, 0.1 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in chloroform and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.070 g, 79%) as a yellow oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.26-7.16 (5H, m, Ph-*H*), 5.58 (1H, t, *J* = 6.9 Hz, OC*H*CH_2), 1.98 (3H, s, COCH_3), 1.86-1.68 (2H, m, CHC$H_2$$CH_3$), 0.79 (3H, t, *J* = 7.4 Hz, CH_2CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.47, 140.63, 128.45, 127.88, 126.64, 77.42, 29.37, 21.30, 9.97; IR (film, cm^{-1}): ν_{max} = 1731 (C=O), 1689, 1495, 1455.

(±)-Oct-1-en-3-yl acetate (473)[279]



1-Octen-3-ol (**465**) (0.08 mL, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and DBN (**6**) (0.01 mL, 0.1 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product was dissolved in chloroform and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.054 g, 63%) as a brown solid. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 5.82-5.70 (1H, m, OCHC*H*CH_2), 5.24-5.12 (3H, m, OC*H*CHCH_2), 2.04 (3H, s, COCH_3), 1.70-1.49 (2H, m, OCHCH_2), 1.35-1.24 (6H, m, $(CH_2)_3CH_3$), 0.87 (3H, t, *J* = 6.5 Hz, $(CH_2)_3$CH_3); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 170.49, 136.78, 116.59, 74.99, 34.26, 31.66, 24.82, 22.62, 21.35, 14.08; IR (film, cm^{-1}): ν_{max} = 2929, 2860, 1737 (C=O), 1668 (C=C).

(±)-2,3-Dihydro-1*H*-inden-1-yl acetate (474)[280]



1-Indanol (**466**) (0.067 g, 0.5 mmol) was added to a solution of *N*-acetyl DBN·BPh_4 (**360**) (0.316 g, 0.65 mmol) and DBN (**6**) (0.01 mL, 0.1 mmol) in acetonitrile (2 mL) and the resulting solution was heated at 80 °C for 16 hours according to the general procedure. The crude product

was dissolved in chloroform and the excess salts were filtered off. The solution was washed with NH_4Cl and brine before being dried over $MgSO_4$, filtered, and concentrated to give the title compound (0.062 g, 70%) as a colourless oil. ^{1}H NMR (300 MHz; $CDCl_3$): δ_H = 7.34 (1H, d, *J* = 7.3 Hz, Ar-*H*), 7.22-7.12 (3H, m, Ar-*H*), 6.12 (1H, dd, *J* = 7.0, 3.7 Hz, OC*H*CH^{A}H^B), 3.09-2.98 (1H, m, OCHCH^{A}H^{B}C*H*^{c}H^D), 2.85-2.75 (1H, m, OCHCH^{A}H^{B}CH^c*H*^{D}), 2.48-2.36 (1H, m, OCHC*H*^{A}H^B), 2.07-1.96 (1H, m, OCHCH^A*H*^{B}), 1.98 (3H, s, COC*H*$_3$); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ_C = 171.25, 144.53, 141.13, 129.06, 126.81, 125.65, 124.92, 78.46, 32.39, 30.30, 21.44; IR (film, cm^{-1}): ν_{max} = 1730 (C=O), 1479, 1462.

5.4 Iodide as a Nucleophilic Catalyst

5.4.1 General Procedure for the LiI Catalysed Acylation of *N*-Methylpyrrole

Lithium iodide (0.134 g, 1 mmol) and powdered 4Å molecular sieves were added to a Radleys carousel tube (150 × 24 mm fitted with gas-tight threaded PTFE caps with a suba-seal, sidearm and inlet valve) and purged with nitrogen. Anhydrous ethyl acetate (1 mL), *N*-methylpyrrole (**167**) (0.12 mL, 1.3 mmol), and the appropriate acyl chloride (1 mmol) were added and the sealed carousel tube was heated at 80 °C for one hour. The reaction mixture was allowed to cool to room temperature before being filtered and concentrated under reduced pressure. Conversions were obtained by ^{1}H NMR spectroscopic analysis of the crude reaction mixture using 2,5-dimethylfuran as an internal standard.

6 Appendix 1: X-Ray Crystal Data

6.1 X-Ray Crystal Structure Data for *N*-Benzoyl DBN·BPh_4

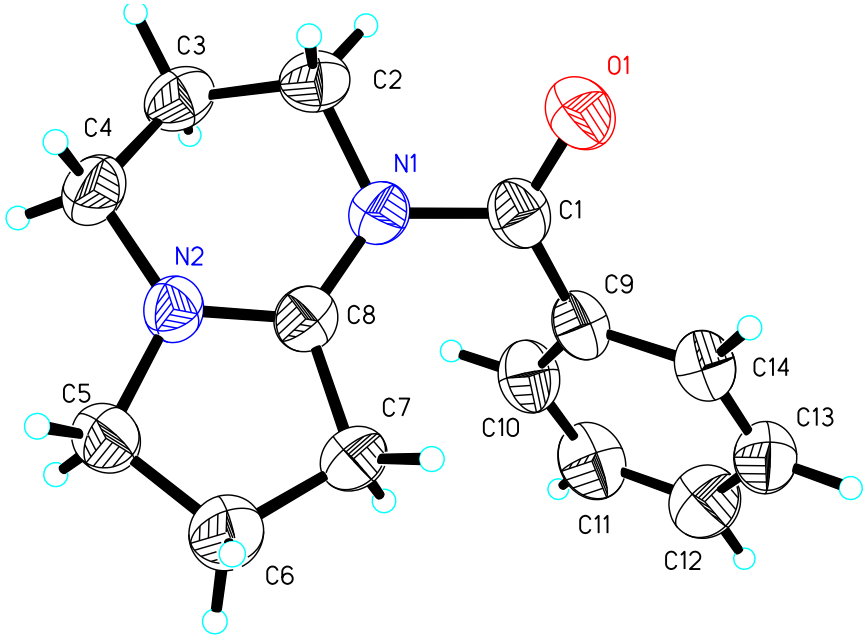


Figure 13. X-ray crystal structure of *N*-benzoyl DBN·BPh_4 (**275**). Ellipsoids shown at 50 % probability level. Half a molecule of hexane solvent has been removed for clarity (this was left isotropic) and a BPh_4 counter-ion has been removed for clarity. The crystal did not diffract to high angle and the data was truncated to θ = 24.12. The majority of .cif errors are related to this. The hexane was restrained by DFIX and DANG instructions to conform to norm. Interestingly an adsorption correction was significant and this was applied to final solution (non-adsorbed data Rint = 0.1342 and wR2 = 0.2612).

Table 24. Crystal data and structure refinement for *N*-benzoyl DBN·BPh_4 (**275**).

Empirical formula	$C_{41}H_{44}BN_2O$	
Formula weight	591.59	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
space group	$P2_1/n$	
Unit cell dimensions	a = 10.969(4) Å	α = 90°
	b = 19.154(3) Å	β = 104.199(14)°
	c = 15.685(2) Å	γ = 90°
Volume	3194.7(13) $Å^3$	
Z	4	
Calculated density	1.230 Mg/m^3	
Absorption coefficient	0.072 mm^{-1}	
F(000)	1268	
Crystal size	0.10 × 0.10 × 0.10 mm	
Theta range for data collection	3.59 to 24.12 °	
Limiting indices	$-12 \leq h \leq 12$, $-22 \leq k \leq 22$, $-17 \leq l \leq 18$	
Reflections collected	23047	
Independent Reflections	5057 [R(int) = 0.1163]	
Completeness to theta= 24.12	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9928 and 0.9928	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5057 / 5 / 392	
Goodness-of-fit on F^2	1.040	
Final R indices [I>2sigma(I)]	R1 = 0.0796, wR2 = 0.2174	
R indices (all data)	R1 = 0.1218, wR2 = 0.2585	
Extinction coefficient	0.016(3)	
Largest diff. peak and hole	0.898 and -0.525 e. $Å^{-3}$	

Table 25. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for *N*-benzoyl DBN·BPh_4 (**275**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	1246(3)	120(2)	617(2)	55(1)
N(1)	-1207(3)	887(2)	1716(2)	43(1)
C(1)	-700(4)	315(2)	1343(3)	46(1)
B(1)	2990(5)	2113(2)	239(3)	42(1)
N(2)	-1025(3)	1945(2)	2448(2)	41(1)
C(2)	-2565(4)	1023(2)	1361(3)	47(1)
C(3)	-3077(4)	1393(2)	2049(3)	49(1)
C(4)	-2376(4)	2064(2)	2313(3)	51(1)
C(5)	-110(4)	2454(2)	2922(3)	52(1)
C(6)	1131(5)	2183(3)	2815(4)	62(1)
C(7)	895(4)	1449(2)	2463(3)	50(1)
C(8)	-501(4)	1395(2)	2192(2)	40(1)
C(9)	390(4)	-65(2)	1889(3)	44(1)
C(10)	471(5)	-229(2)	2758(3)	54(1)
C(11)	1435(5)	-649(3)	3215(3)	62(1)
C(12)	2327(5)	-893(3)	2811(3)	61(1)
C(13)	2260(5)	-729(2)	1943(3)	57(1)
C(14)	1290(4)	-320(2)	1474(3)	48(1)
C(15)	1497(4)	2233(2)	175(2)	39(1)
C(16)	1025(4)	2865(2)	409(3)	51(1)
C(17)	-223(5)	2948(2)	431(3)	58(1)
C(18)	-1066(5)	2409(2)	210(3)	52(1)
C(19)	-639(4)	1777(2)	-20(3)	46(1)
C(20)	610(4)	1692(2)	-31(3)	45(1)
C(21)	3548(4)	1834(2)	1254(3)	40(1)
C(22)	3968(4)	2302(2)	1956(3)	47(1)
C(23)	4343(4)	2088(3)	2819(3)	51(1)

Table 25 continued

	x	y	z	U(eq)
C(24)	4324(4)	1389(3)	3027(3)	52(1)
C(25)	3913(4)	914(3)	2368(3)	52(1)
C(26)	3534(4)	1134(2)	1496(3)	45(1)
C(27)	3737(4)	2822(2)	56(3)	44(1)
C(28)	5035(4)	2885(2)	392(3)	52(1)
C(29)	5717(5)	3461(3)	244(3)	59(1)
C(30)	5127(5)	3995(2)	-286(3)	59(1)
C(31)	3844(5)	3946(2)	-649(3)	55(1)
C(32)	3179(4)	3373(2)	-486(3)	48(1)
C(33)	3236(4)	1546(2)	-495(3)	43(1)
C(34)	4335(5)	1143(2)	-349(3)	55(1)
C(35)	4633(6)	715(2)	-979(4)	66(2)
C(36)	3825(6)	668(3)	-1803(4)	71(2)
C(37)	2740(5)	1047(2)	-1973(3)	60(1)
C(38)	2446(5)	1476(2)	-1330(3)	49(1)
C(100)	-143(7)	4880(6)	391(4)	148(4)
C(101)	-1505(8)	4827(7)	272(7)	174(4)
C(102)	-1682(17)	4700(14)	1191(11)	343(12)

Table 26. Bond lengths for *N*-benzoyl DBN·BPh_4 (**275**).

Bond	Length (Å)	Bond	Length (Å)
O(1)-C(1)	1.208(5)	N(1)-C(8)	1.349(5)
N(1)-C(1)	1.419(5)	N(1)-C(2)	1.480(5)
C(1)-C(9)	1.480(6)	B(1)-C(15)	1.632(6)
B(1)-C(21)	1.647(6)	B(1)-C(27)	1.649(6)
B(1)-C(33)	1.653(6)	N(2)-C(8)	1.310(5)
N(2)-C(4)	1.462(5)	N(2)-C(5)	1.465(5)
C(2)-C(3)	1.510(6)	C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900	C(3)-C(4)	1.503(6)
C(3)-H(3A)	0.9900	C(3)-H(3B)	0.9900
C(4)-H(4A)	0.9900	C(4)-H(4B)	0.9900
C(5)-C(6)	1.504(6)	C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900	C(6)-C(7)	1.509(7)
C(6)-H(6A)	0.9900	C(6)-H(6B)	0.9900
C(7)-C(8)	1.489(6)	C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900	C(9)-C(10)	1.380(6)
C(9)-C(14)	1.397(6)	C(10)-C(11)	1.381(7)
C(10)-H(10)	0.9500	C(11)-C(12)	1.371(7)
C(11)-H(11)	0.9500	C(12)-C(13)	1.382(7)
C(12)-H(12)	0.9500	C(13)-C(14)	1.378(6)
C(13)-H(13)	0.9500	C(14)-H(14)	0.9500
C(15)-C(16)	1.400(6)	C(15)-C(20)	1.404(6)
C(16)-C(17)	1.387(6)	C(16)-H(16)	0.9500
C(17)-C(18)	1.373(7)	C(17)-H(17)	0.9500
C(18)-C(19)	1.378(6)	C(18)-H(18)	0.9500
C(19)-C(20)	1.384(6)	C(19)-H(19)	0.9500
C(20)-H(20)	0.9500	C(21)-C(26)	1.395(6)
C(21)-C(22)	1.407(6)	C(22)-C(23)	1.376(6)
C(22)-H(22)	0.9500	C(23)-C(24)	1.380(7)

Table 26 continued

Bond	Length (Å)	Bond	Length (Å)
C(23)-H(23)	0.9500	C(24)-C(25)	1.368(7)
C(24)-H(24)	0.9500	C(25)-C(26)	1.394(6)
C(25)-H(25)	0.9500	C(26)-H(26)	0.9500
C(27)-C(28)	1.397(6)	C(27)-C(32)	1.398(6)
C(28)-C(29)	1.384(6)	C(28)-H(28)	0.9500
C(29)-C(30)	1.375(7)	C(29)-H(29)	0.9500
C(30)-C(31)	1.386(7)	C(30)-H(30)	0.9500
C(31)-C(32)	1.375(6)	C(31)-H(31)	0.9500
C(32)-H(32)	0.9500	C(33)-C(38)	1.388(6)
C(33)-C(34)	1.402(6)	C(34)-C(35)	1.383(7)
C(34)-H(34)	0.9500	C(35)-C(36)	1.379(8)
C(35)-H(35)	0.9500	C(36)-C(37)	1.364(8)
C(36)-H(36)	0.9500	C(37)-C(38)	1.397(6)
C(37)-H(37)	0.9500	C(38)-H(38)	0.9500
C(100)-C(100)#1	1.414(9)	C(100)-C(101)	1.464(8)
C(100)-H(10A)	0.9900	C(100)-H(10B)	0.9900
C(101)-C(102)	1.520(9)	C(101)-H(10C)	0.9900
C(101)-H(10D)	0.9900	C(102)-H(10E)	0.9800
C(102)-H(10F)	0.9800	C(102)-H(10G)	0.9800

Table 27. Bond Angles for *N*-benzoyl DBN·BPh_4 (**275**).

Bond	Angle (°)	Bond	Angle (°)
C(8)-N(1)-C(1)	123.7(4)	C(8)-N(1)-C(2)	118.1(3)
C(1)-N(1)-C(2)	116.1(3)	O(1)-C(1)-N(1)	118.3(4)
O(1)-C(1)-C(9)	122.5(4)	N(1)-C(1)-C(9)	118.9(4)
C(15)-B(1)-C(21)	103.6(3)	C(15)-B(1)-C(27)	114.0(4)
C(21)-B(1)-C(27)	110.6(3)	C(15)-B(1)-C(33)	112.5(3)
C(21)-B(1)-C(33)	112.1(3)	C(27)-B(1)-C(33)	104.2(3)
C(8)-N(2)-C(4)	125.9(4)	C(8)-N(2)-C(5)	113.2(4)
C(4)-N(2)-C(5)	120.9(3)	N(1)-C(2)-C(3)	109.2(3)
N(1)-C(2)-H(2A)	109.8	C(3)-C(2)-H(2A)	109.8
N(1)-C(2)-H(2B)	109.8	C(3)-C(2)-H(2B)	109.8
H(2A)-C(2)-H(2B)	108.3	C(4)-C(3)-C(2)	110.1(4)
C(4)-C(3)-H(3A)	109.6	C(2)-C(3)-H(3A)	109.6
C(4)-C(3)-H(3B)	109.6	C(2)-C(3)-H(3B)	109.6
H(3A)-C(3)-H(3B)	108.2	N(2)-C(4)-C(3)	109.8(4)
N(2)-C(4)-H(4A)	109.7	C(3)-C(4)-H(4A)	109.7
N(2)-C(4)-H(4B)	109.7	C(3)-C(4)-H(4B)	109.7
H(4A)-C(4)-H(4B)	108.2	N(2)-C(5)-C(6)	103.9(3)
N(2)-C(5)-H(5A)	111.0	C(6)-C(5)-H(5A)	111.0
N(2)-C(5)-H(5B)	111.0	C(6)-C(5)-H(5B)	111.0
H(5A)-C(5)-H(5B)	109.0	C(5)-C(6)-C(7)	106.5(4)
C(5)-C(6)-H(6A)	110.4	C(7)-C(6)-H(6A)	110.4
C(5)-C(6)-H(6B)	110.4	C(7)-C(6)-H(6B)	110.4
H(6A)-C(6)-H(6B)	108.6	C(8)-C(7)-C(6)	104.0(4)
C(8)-C(7)-H(7A)	111.0	C(6)-C(7)-H(7A)	111.0
C(8)-C(7)-H(7B)	111.0	C(6)-C(7)-H(7B)	111.0
H(7A)-C(7)-H(7B)	109.0	N(2)-C(8)-N(1)	120.9(4)
N(2)-C(8)-C(7)	110.7(4)	N(1)-C(8)-C(7)	128.3(4)
C(10)-C(9)-C(14)	119.9(4)	C(10)-C(9)-C(1)	122.1(4)

Table 27 continued

Bond	Angle (°)	Bond	Angle (°)
C(14)-C(9)-C(1)	117.7(4)	C(9)-C(10)-C(11)	120.1(4)
C(9)-C(10)-H(10)	120.0	C(11)-C(10)-H(10)	120.0
C(12)-C(11)-C(10)	120.1(4)	C(12)-C(11)-H(11)	120.0
C(10)-C(11)-H(11)	120.0	C(11)-C(12)-C(13)	120.4(5)
C(11)-C(12)-H(12)	119.8	C(13)-C(12)-H(12)	119.8
C(14)-C(13)-C(12)	120.2(4)	C(14)-C(13)-H(13)	119.9
C(12)-C(13)-H(13)	119.9	C(13)-C(14)-C(9)	119.4(4)
C(13)-C(14)-H(14)	120.3	C(9)-C(14)-H(14)	120.3
C(16)-C(15)-C(20)	114.7(4)	C(16)-C(15)-B(1)	122.5(4)
C(20)-C(15)-B(1)	122.5(4)	C(17)-C(16)-C(15)	122.5(4)
C(17)-C(16)-H(16)	118.7	C(15)-C(16)-H(16)	118.7
C(18)-C(17)-C(16)	120.9(4)	C(18)-C(17)-H(17)	119.5
C(16)-C(17)-H(17)	119.5	C(17)-C(18)-C(19)	118.5(4)
C(17)-C(18)-H(18)	120.8	C(19)-C(18)-H(18)	120.8
C(18)-C(19)-C(20)	120.5(4)	C(18)-C(19)-H(19)	119.8
C(20)-C(19)-H(19)	119.8	C(19)-C(20)-C(15)	122.9(4)
C(19)-C(20)-H(20)	118.6	C(15)-C(20)-H(20)	118.6
C(26)-C(21)-C(22)	115.0(4)	C(26)-C(21)-B(1)	123.2(4)
C(22)-C(21)-B(1)	121.5(4)	C(23)-C(22)-C(21)	122.7(4)
C(23)-C(22)-H(22)	118.6	C(21)-C(22)-H(22)	118.6
C(22)-C(23)-C(24)	120.3(4)	C(22)-C(23)-H(23)	119.9
C(24)-C(23)-H(23)	119.9	C(25)-C(24)-C(23)	119.2(4)
C(25)-C(24)-H(24)	120.4	C(23)-C(24)-H(24)	120.4
C(24)-C(25)-C(26)	120.2(4)	C(24)-C(25)-H(25)	119.9
C(26)-C(25)-H(25)	119.9	C(25)-C(26)-C(21)	122.6(4)
C(25)-C(26)-H(26)	118.7	C(21)-C(26)-H(26)	118.7
C(28)-C(27)-C(32)	114.7(4)	C(28)-C(27)-B(1)	120.6(4)
C(32)-C(27)-B(1)	124.5(4)	C(29)-C(28)-C(27)	123.2(4)
C(29)-C(28)-H(28)	118.4	C(27)-C(28)-H(28)	118.4

Table 27 continued

Bond	Angle (°)	Bond	Angle (°)
C(30)-C(29)-C(28)	120.0(5)	C(30)-C(29)-H(29)	120.0
C(28)-C(29)-H(29)	120.0	C(29)-C(30)-C(31)	118.6(4)
C(29)-C(30)-H(30)	120.7	C(31)-C(30)-H(30)	120.7
C(32)-C(31)-C(30)	120.6(5)	C(32)-C(31)-H(31)	119.7
C(30)-C(31)-H(31)	119.7	C(31)-C(32)-C(27)	122.8(4)
C(31)-C(32)-H(32)	118.6	C(27)-C(32)-H(32)	118.6
C(38)-C(33)-C(34)	114.4(4)	C(38)-C(33)-B(1)	123.4(4)
C(34)-C(33)-B(1)	121.9(4)	C(35)-C(34)-C(33)	123.7(5)
C(35)-C(34)-H(34)	118.2	C(33)-C(34)-H(34)	118.2
C(36)-C(35)-C(34)	119.8(5)	C(36)-C(35)-H(35)	120.1
C(34)-C(35)-H(35)	120.1	C(37)-C(36)-C(35)	118.6(5)
C(37)-C(36)-H(36)	120.7	C(35)-C(36)-H(36)	120.7
C(36)-C(37)-C(38)	121.1(5)	C(36)-C(37)-H(37)	119.5
C(38)-C(37)-H(37)	119.5	C(33)-C(38)-C(37)	122.5(5)
C(33)-C(38)-H(38)	118.8	C(37)-C(38)-H(38)	118.8
C(100)#1-C(100)-C(101)	110.4(8)	C(100)#1-C(100)-H(10A)	109.6
C(101)-C(100)-H(10A)	109.6	C(100)#1-C(100)-H(10B)	109.6
C(101)-C(100)-H(10B)	109.6	H(10A)-C(100)-H(10B)	108.1
C(100)-C(101)-C(102)	104.7(8)	C(100)-C(101)-H(10C)	110.8
C(102)-C(101)-H(10C)	110.8	C(100)-C(101)-H(10D)	110.8
C(102)-C(101)-H(10D)	110.8	H(10C)-C(101)-H(10D)	108.9
C(101)-C(102)-H(10E)	109.5	C(101)-C(102)-H(10F)	109.5
H(10E)-C(102)-H(10F)	109.5	C(101)-C(102)-H(10G)	109.5
H(10E)-C(102)-H(10G)	109.5	H(10F)-C(102)-H(10G)	109.5

Table 28. Anisotropic displacement parameters ($Å^2 \times 10^3$) for *N*-benzoyl DBN·BPh_4 (**275**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U11 + ... + 2hka^*b^*U12]$.

	U11	U22	U33	U23	U13	U12
O(1)	64(2)	55(2)	45(2)	-4(1)	12(2)	0(2)
N(1)	39(2	45(2)	45(2)	-1(2)	13(2)	2(2)
C(1)	54(3)	46(2)	42(2)	-2(2)	18(2)	-4(2)
B(1)	42(3)	41(2)	46(3)	-1(2)	12(2)	-2(2)
N(2)	41(2)	44(2)	42(2)	-3(2)	16(2)	2(2)
C(2)	38(2)	52(3)	49(2)	1(2)	10(2)	-4(2)
C(3)	38(3)	61(3)	51(2)	5(2)	15(2)	2(2)
C(4)	42(3)	58(3)	55(3)	-3(2)	17(2)	9(2)
C(5)	48(3)	50(3)	58(3)	-10(2)	15(2)	-6(2)
C(6)	50(3)	59(3)	79(3)	-11(3)	22(2)	-5(2)
C(7)	36(3)	59(3)	58(3)	-8(2)	15(2)	0(2)
C(8)	41(2)	45(2)	37(2)	4(2)	16(2)	0(2)
C(9)	57(3)	36(2)	42(2)	-3(2)	17(2)	-3(2)
C(10)	67(3)	51(3)	47(3)	0(2)	20(2)	2(2)
C(11)	85(4)	54(3)	47(3)	7(2)	18(3)	4(3)
C(12)	66(3)	51(3)	65(3)	12(2)	14(3)	8(2)
C(13)	58(3)	54(3)	62(3)	-7(2)	19(2)	3(2)
C(14)	56(3)	44(2)	45(2)	-3(2)	17(2)	-1(2)
C(15)	43(2)	39(2)	35(2)	0(2)	10(2)	2(2)
C(16)	54(3)	46(2)	57(3)	-10(2)	20(2)	-6(2)
C(17)	59(3)	46(3)	75(3)	-3(2)	31(3)	13(2)
C(18)	50(3)	53(3)	58(3)	8(2)	22(2)	7(2)
C(19)	41(3)	52(3)	47(2)	0(2)	15(2)	-5(2)
C(20)	49(3)	39(2)	50(2)	1(2)	20(2)	0(2)
C(21)	29(2)	45(2)	49(2)	-3(2)	14(2)	1(2)
C(22)	41(3)	49(2)	53(3)	-2(2)	14(2)	2(2)
C(23)	44(3)	64(3)	47(2)	-7(2)	15(2)	1(2)
C(24)	42(3)	68(3)	50(3)	5(2)	16(2)	1(2)

Table 28 continued

	U11	U22	U33	U23	U13	U12
C(25)	44(3)	54(3)	61(3)	14(2)	17(2)	0(2)
C(26)	38(2)	47(2)	54(3)	3(2)	16(2)	0(2)
C(27)	45(3)	44(2)	45(2)	-3(2)	16(2)	2(2)
C(28)	48(3)	50(3)	61(3)	5(2)	17(2)	-1(2)
C(29)	54(3)	59(3)	68(3)	5(2)	22(2)	-11(2)
C(30)	73(4)	51(3)	58(3)	-3(2)	25(3)	-18(2)
C(31)	69(4)	48(3)	49(3)	7(2)	18(2)	-2(2)
C(32)	51(3)	49(2)	44(2)	-2(2)	14(2)	-3(2)
C(33)	46(3)	39(2)	48(2)	-1(2)	21(2)	-5(2)
C(34)	54(3)	56(3)	62(3)	-2(2)	26(2)	4(2)
C(35)	72(4)	51(3)	93(4)	1(3)	52(3)	9(3)
C(36)	98(5)	49(3)	84(4)	-15(3)	60(4)	-9(3)
C(37)	73(4)	56(3)	59(3)	-12(2)	32(3)	-21(3)
C(38)	58(3)	42(2)	51(3)	-5(2)	25(2)	-7(2)

6.2 X-Ray Crystal Structure Data for *N*-Hydrocinnamoyl DBN·BPh_4

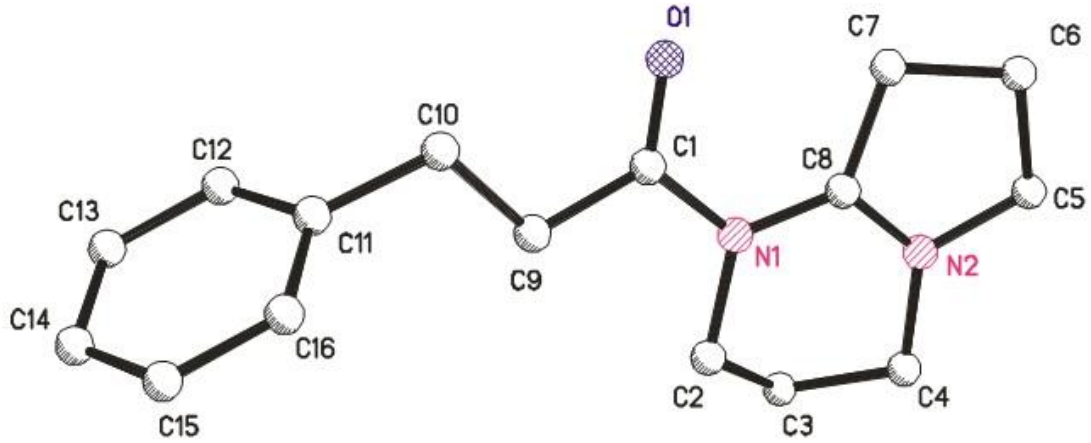


Figure 14. X-ray crystal structure of *N*-hydrocinnamoyl DBN·BPh_4 (**362**). The H atoms, BPh_4 counter-ion, and one molecule of CH_2Cl_2 have been removed for clarity.

Table 29. Crystal data and structure refinement for *N*-hydrocinnamoyl DBN·BPh_4 (**362**).

Empirical formula	$C_{41}H_{43}BCl_2N_2O$	
Formula weight	661.48	
Temperature	150(2) K	
Wavelength	0.71073 A	
Crystal system	Orthorhombic	
space group	*Pcan*	
Unit cell dimensions	a = 17.718(10) Å	α = 90°
	b = 19.401(10) Å	β = 90°
	c = 20.336(2) Å	γ = 90°
Volume	6990.44(9) $Å^3$	
Z	8	
Calculated density	1.257 Mg/m^3	
Absorption coefficient	0.221 mm^{-1}	
F(000)	2800	
Crystal size	0.30 × 0.20 × 0.20 mm	
Theta range for data collection	3.61 to 27.48 °	
Limiting indices	$-22 \leq h \leq 23$, $-25 \leq k \leq 25$, $-26 \leq l \leq 26$	
Reflections collected	115031	
Independent Reflections	7989 [R(int) = 0.0666]	
Completeness to theta= 24.12	99.7 %	
Absorption correction	Multi-scan	
Max. and min. transmission	0.9571 and 0.9366	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7989 / 0 / 424	
Goodness-of-fit on F^2	1.023	
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.0936	
R indices (all data)	R1 = 0.0605, wR2 = 0.1049	
Largest diff. peak and hole	0.276 and -0.457 e. $Å^{-3}$	

Table 30. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for *N*-hydrocinnamoyl DBN·BPh_4 (**362**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl(1)	7336(1)	4359(1)	3283(1)	57(1)
O(1)	10083(1)	3799(1)	65(1)	38(1)
N(1)	8876(1)	3473(1)	-211(1)	24(1)
C(1)	9608(1)	3351(1)	61(1)	26(1)
B(1)	8067(1)	2008(1)	2116(1)	20(1)
Cl(2)	8789(1)	3955(1)	3840(1)	44(1)
N(2)	8069(1)	4165(1)	-827(1)	27(1)
C(2)	8289(1)	2924(1)	-171(1)	29(1)
C(3)	7505(1)	3225(1)	-229(1)	35(1)
C(4)	7439(1)	3678(1)	-830(1)	32(1)
C(5)	8010(1)	4827(1)	-1176(1)	36(1)
C(6)	8798(1)	5137(1)	-1120(1)	47(1)
C(7)	9228(1)	4671(1)	-633(1)	37(1)
C(8)	8718(1)	4063(1)	-540(1)	25(1)
C(9)	9745(1)	2639(1)	331(1)	26(1)
C(10)	10565(1)	2548(1)	553(1)	32(1)
C(11)	10682(1)	1863(1)	893(1)	28(1)
C(12)	10692(1)	1822(1)	1575(1)	32 (1)
C(13)	10755(1)	1193(1)	1890(1)	39(1)
C(14)	10819(1)	594(1)	1533(1)	43(1)
C(15)	10829(1)	626(1)	851(1)	43(1)
C(16)	10760(1)	1255(1)	534(1)	35(1)
C(17)	8073(1)	1601(1)	1406(1)	22(1)
C(18)	8700(1)	1241(1)	1159(1)	26(1)
C(19)	8710(1)	956(1)	531(1)	34(1)
C(20)	8093(1)	1028(1)	117(1)	38(1)
C(21)	7467(1)	1387(1)	339(1)	34(1)
C(22)	7462(1)	1663(1)	969(1)	27(1)

Table 30 continued

	x	y	z	U(eq)
C(23)	7222(1)	1989(1)	2450(1)	23(1)
C(24)	6766(1)	1400(1)	2417(1)	29(1)
C(25)	6068(1)	1358(1)	2732(1)	36(1)
C(26)	5796(1)	1907(1)	3095(1)	36(1)
C(27)	6235(1)	2492(1)	3147(1)	34(1)
C(28)	6932(1)	2529(1)	2832(1)	28(1)
C(29)	8623(1)	1661(1)	2672(1)	20(1)
C(30)	8751(1)	950(1)	2715(1)	24(1)
C(31)	9202(1)	652(1)	3199(1)	28(1)
C(32)	9540(1)	1063(1)	3672(1)	29(1)
C(33)	9404(1)	1766(1)	3662(1)	28(1)
C(34)	8953(1)	2053(1)	3176(1)	23(1)
C(35)	8333(1)	2794(1)	1913(1)	21(1)
C(36)	9091(1)	3005(1)	1932(1)	24(1)
C(37)	9332(1)	3639(1)	1686(1)	30(1)
C(38)	8816(1)	4092(1)	1411(1)	34(1)
C(39)	8062(1)	3908(1)	1389(1)	33(1)
C(40)	7829(1)	3270(1)	1634(1)	27(1)
C(41)	8288(1)	4183(1)	3119(1)	42(1)

Table 31. Bond lengths for *N*-hydrocinnamoyl DBN·BPh_4 (**362**).

Bond	Length (Å)	Bond	Length (Å)
Cl(1)-C(41)	1.753(2)	O(1)-C(1)	1.2093(18)
N(1)-C(8)	1.3557(19)	N(1)-C(1)	1.4294(18)
N(1)-C(2)	1.4928(18)	C(1)-C(9)	1.505(2)
B(1)-C(29)	1.644(2)	B(1)-C(23)	1.645(2)
B(1)-C(17)	1.646(2)	B(1)-C(35)	1.648(2)
Cl(2)-C(41)	1.7717(19)	N(2)-C(8)	1.3037(19)
N(2)-C(4)	1.4631(19)	N(2)-C(5)	1.471(2)
C(2)-C(3)	1.511(2)	C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900	C(3)-C(4)	1.509(2)
C(3)-H(3A)	0.9900	C(3)-H(3B)	0.9900
C(4)-H(4A)	0.9900	C(4)-H(4B)	0.9900
C(5)-C(6)	1.526(2)	C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900	C(6)-C(7)	1.541(2)
C(6)-H(6A)	0.9900	C(6)-H(6B)	0.9900
C(7)-C(8)	1.498(2)	C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900	C(9)-C(10)	1.533(2)
C(9)-H(9A)	0.9900	C(9)-H(9B)	0.9900
C(10)-C(11)	1.511(2)	C(10)-H(10A)	0.9900
C(10)-H(10B)	0.9900	C(11)-C(12)	1.391(2)
C(11)-C(16)	1.393(2)	C(12)-C(13)	1.382(2)
C(12)-H(12)	0.9500	C(13)-C(14)	1.376(3)
C(13)-H(13)	0.9500	C(14)-C(15)	1.389(3)
C(14)-H(14)	0.9500	C(15)-C(16)	1.387(2)
C(15)-H(15)	0.9500	C(16)-H(16)	0.9500
C(17)-C(18)	1.405(2)	C(17)-C(22)	1.405(2)
C(18)-C(19)	1.393(2)	C(18)-H(18)	0.9500
C(19)-C(20)	1.387(2)	C(19)-H(19)	0.9500
C(20)-C(21)	1.385(2)	C(20)-H(20)	0.9500
C(21)-C(22)	1.389(2)	C(21)-H(21)	0.9500

Table 31 continued

Bond	Length (Å)	Bond	Length (Å)
C(22)-H(22)	0.9500	C(23)-C(28)	1.401(2)
C(23)-C(24)	1.401(2)	C(24)-C(25)	1.395(2)
C(24)-H(24)	0.9500	C(25)-C(26)	1.383(3)
C(25)-H(25)	0.9500	C(26)-C(27)	1.380(2)
C(26)-H(26)	0.9500	C(27)-C(28)	1.392(2)
C(27)-H(27)	0.9500	C(28)-H(28)	0.9500
C(29)-C(30)	1.4026(19)	C(29)-C(34)	1.4029(19)
C(30)-C(31)	1.392(2)	C(30)-H(30)	0.9500
C(31)-C(32)	1.386(2)	C(31)-H(31)	0.9500
C(32)-C(33)	1.386(2)	C(32)-H(32)	0.9500
C(33)-C(34)	1.388(2)	C(33)-H(33)	0.9500
C(34)-H(34)	0.9500	C(35)-C(40)	1.405(2)
C(35)-C(36)	1.405(2)	C(36)-C(37)	1.395(2)
C(36)-H(36)	0.9500	C(37)-C(38)	1.384(2)
C(37)-H(37)	0.9500	C(38)-C(39)	1.384(2)
C(38)-H(38)	0.9500	C(39)-C(40)	1.395(2)
C(39)-H(39)	0.9500	C(40)-H(40)	0.9500
C(41)-H(41A)	0.9900	C(41)-H(41B)	0.9900

Table 32. Bond Angles for *N*-hydrocinnamoyl DBN·BPh_4 (**362**).

Bond	Angle (°)	Bond	Angle (°)
C(8)-N(1)-C(1)	121.30(12)	C(8)-N(1)-C(2)	119.07(12)
C(1)-N(1)-C(2)	119. 50(12)	O(1)-C(1)-N(1)	120.87(13)
O(1)-C(1)-C(9)	123.05(13)	N(1)-C(1)-C(9)	116.08(12)
C(29)-B(1)-C(23)	104.60(11)	C(29)-B(1)-C(17)	113.74(11)
C(23)-B(1)-C(17)	110.93(11)	C(29)-B(1)-C(35)	112.33(11)
C(23)-B(1)-C(35)	112.64(11)	C(17)-B(1)-C(35)	102.86(11)
C(8)-N(2)-C(4)	125.22(13)	C(8)-N(2)-C(5)	114.31(12)
C(4)-N(2)-C(5)	120.46(12)	N(1)-C(2)-C(3)	111.11(13)
N(1)-C(2)-H(2A)	109.4	C(3)-C(2)-H(2A)	109.4
N(1)-C(2)-H(2B)	109.4	C(3)-C(2)-H(2B)	109.4
H(2A)-C(2)-H(2B)	108.0	C(4)-C(3)-C(2)	111.10(13)
C(4)-C(3)-H(3A)	109.4	C(2)-C(3)-H(3A)	109.4
C(4)-C(3)-H(3B)	109.4	C(2)-C(3)-H(3B)	109.4`
H(3A)-C(3)-H(3B)	108.0	N(2)-C(4)-C(3)	108.30(12)
N(2)-C(4)-H(4A)	110.0	C(3)-C(4)-H(4A)	110.0
N(2)-C(4)-H(4B)	110.0	C(3)-C(4)-H(4B)	110.0
H(4A)-C(4)-H(4B)	108.4	N(2)-C(5)-C(6)	104.00(13)
N(2)-C(5)-H(5A)	111.0	C(6)-C(5)-H(5A)	111.0
N(2)-C(5)-H(5B)	111.0	C(6)-C(5)-H(5B)	111.0
H(5A)-C(5)-H(5B)	109.0	C(5)-C(6)-C(7)	105.63(14)
C(5)-C(6)-H(6A)	110.6	C(7)-C(6)-H(6A)	110.6
C(5)-C(6)-H(6B)	110.6	C(7)-C(6)-H(6B)	110.6
H(6A)-C(6)-H(6B)	108.7	C(8)-C(7)-C(6)	104.18(13)
C(8)-C(7)-H(7A)	110.9	C(6)-C(7)-H(7A)	110.9
C(8)-C(7)-H(7B)	110.9	C(6)-C(7)-H(7B)	110.9
H(7A)-C(7)-H(7B)	108.9	N(2)-C(8)-N(1)	122.09(13)
N(2)-C(8)-C(7)	110.84(13)	N(1)-C(8)-C(7)	127.07(13)
C(1)-C(9)-C(10)	111.47(12)	C(1)-C(9)-H(9A)	109.3
C(10)-C(9)-H(9A)	109.3	C(1)-C(9)-H(9B)	109.3

Table 32 continued

Bond	Angle (°)	Bond	Angle (°)
C(10)-C(9)-H(9B)	109.3	H(9A)-C(9)-H(9B)	108.0
C(11)-C(10)-C(9)	111.45(12)	C(11)-C(10)-H(10A)	109.3
C(9)-C(10)-H(10A)	109.3	C(11)-C(10)-H(10B)	109.3
C(9)-C(10)-H(10B)	109.3	H(10A)-C(10)-H(10B)	108.0
C(12)-C(11)-C(16)	118.21(15)	C(12)-C(11)-C(10)	120.58(14)
C(16)-C(11)-C(10)	121.18(15)	C(13)-C(12)-C(11)	120.98(16)
C(13)-C(12)-H(12)	119.5	C(11)-C(12)-H(12)	119.5
C(14)-C(13)-C(12)	120.47(17)	C(14)-C(13)-H(13)	119.8
C(12)-C(13)-H(13)	119.8	C(13)-C(14)-C(15)	119.44(17)
C(13)-C(14)-H(14)	120.3	C(15)-C(14)-H(14)	120.3
C(16)-C(15)-C(14)	120.15(17)	C(16)-C(15)-H(15)	119.9
C(14)-C(15)-H(15)	119.9	C(15)-C(16)-C(11)	120.70(16)
C(15)-C(16)-H(16)	119.6	C(11)-C(16)-H(16)	119.6
C(18)-C(17)-C(22)	115.19(13)	C(18)-C(17)-B(1)	123.88(12)
C(22)-C(17)-B(1)	120.53(12)	C(19)-C(18)-C(17)	122.42(14)
C(19)-C(18)-H(18)	118.8	C(17)-C(18)-H(18)	118.8
C(20)-C(19)-C(18)	120.40(15)	C(20)-C(19)-H(19)	119.8
C(18)-C(19)-H(19)	119.8	C(21)-C(20)-C(19)	118.97(15)
C(21)-C(20)-H(20)	120.5	C(19)-C(20)-H(20)	120.5
C(20)-C(21)-C(22)	120.02(15)	C(20)-C(21)-H(21)	120.0
C(22)-C(21)-H(21)	120.0	C(21)-C(22)-C(17)	123.00(14)
C(21)-C(22)-H(22)	118.5	C(17)-C(22)-H(22)	118.5
C(28)-C(23)-C(24)	115.14(13)	C(28)-C(23)-B(1)	123.11(12)
C(24)-C(23)-B(1)	121.53(12)	C(25)-C(24)-C(23)	122.48(15)
C(25)-C(24)-H(24)	118.8	C(23)-C(24)-H(24)	118.8
C(26)-C(25)-C(24)	120.56(15)	C(26)-C(25)-H(25)	119.7
C(24)-C(25)-H(25)	119.7	C(27)-C(26)-C(25)	118.55(14)
C(27)-C(26)-H(26)	120.7	C(25)-C(26)-H(26)	120.7
C(26)-C(27)-C(28)	120.45(15)	C(26)-C(27)-H(27)	119.8

Table 32 continued

Bond	Angle (°)	Bond	Angle (°)
C(28)-C(27)-H(27)	119.8	C(27)-C(28)-C(23)	122.80(15)
C(27)-C(28)-H(28)	118.6	C(23)-C(28)-H(28)	118.6
C(30)-C(29)-C(34)	114.86(13)	C(30)-C(29)-B(1)	122.93(12)
C(34)-C(29)-B(1)	121.99(12)	C(31)-C(30)-C(29)	123.02(13)
C(31)-C(30)-H(30)	118.5	C(29)-C(30)-H(30)	118.5
C(32)-C(31)-C(30)	120.06(14)	C(32)-C(31)-H(31)	120.0
C(30)-C(31)-H(31)	120.0	C(33)-C(32)-C(31)	118.69(14)
C(33)-C(32)-H(32)	120.7	C(31)-C(32)-H(32)	120.7
C(32)-C(33)-C(34)	120.40(14)	C(32)-C(33)-H(33)	119.8
C(34)-C(33)-H(33)	119.8	C(33)-C(34)-C(29)	122.87(13)
C(33)-C(34)-H(34)	118.6	C(29)-C(34)-H(34)	118.6
C(40)-C(35)-C(36)	115.31(13)	C(40)-C(35)-B(1)	121.84(12)
C(36)-C(35)-B(1)	122.43(12)	C(37)-C(36)-C(35)	122.60(14)
C(37)-C(36)-H(36)	118.7	C(35)-C(36)-H(36)	118.7
C(38)-C(37)-C(36)	120.20(15)	C(38)-C(37)-H(37)	119.9
C(36)-C(37)-H(37)	119.9	C(37)-C(38)-C(39)	119.09(14)
C(37)-C(38)-H(38)	120.5	C(39)-C(38)-H(38)	120.5
C(38)-C(39)-C(40)	120.15(15)	C(38)-C(39)-H(39)	119.9
C(40)-C(39)-H(39)	119.9	C(39)-C(40)-C(35)	122.64(14)
C(39)-C(40)-H(40)	118.7	C(35)-C(40)-H(40)	118.7
Cl(1)-C(41)-Cl(2)	111.94(10)	Cl(1)-C(41)-H(41A)	109.2
Cl(2)-C(41)-H(41A)	109.2	Cl(1)-C(41)-H(41B)	109.2
Cl(2)-C(41)-H(41B)	109.2	H(41A)-C(41)-H(41B)	107.9

Table 33. Anisotropic displacement parameters ($Å^2 \times 10^3$) for *N*-hydrocinnamoyl DBN·BPh_4 (**362**). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U11 + ... + 2hka^*b^*U12]$.

	U11	U22	U33	U23	U13	U12
Cl(1)	64(1)	50(1)	58(1)	-18(1)	-5(1)	16(1)
O(1)	25(1)	42(1)	47(1)	13(1)	-9(1)	-9(1)
N(1)	19(1)	29(1)	23(1)	1(1)	0(1)	-2(1)
C(1)	20(1)	36(1)	22(1)	2(1)	1(1)	-2(1)
B(1)	19(1)	21(1)	20(1)	-3(1)	-1(1)	0(1)
Cl(2)	57(1)	37(1)	39(1)	0(1)	1(1)	-2(1)
N(2)	23(1)	28(1)	29(1)	-3(1)	-3(1)	2(1)
C(2)	22(1)	35(1)	31(1)	6(1)	-2(1)	-7(1)
C(3)	21(1)	49(1)	34(1)	8(1)	-3(1)	-6(1)
C(4)	23(1)	38(1)	35(1)	1(1)	-7(1)	-4(1)
C(5)	33(1)	26(1)	51(1)	2(1)	-8(1)	4(1)
C(6)	37(1)	30(1)	75(1)	10(1)	-11(1)	1(1)
C(7)	28(1)	29(1)	53(1)	3(1)	-7(1)	-3(1)
C(8)	22(1)	27(1)	24(1)	-5(1)	1(1)	1(1)
C(9)	20(1)	33(1)	24(1)	0(1)	-1(1)	-1(1)
C(10)	21(1)	37(1)	39(1)	4(1)	-2(1)	0(1)
C(11)	16(1)	36(1)	33(1)	0(1)	-3(1)	2(1)
C(12)	21(1)	42(1)	34(1)	-4(1)	-4(1)	3(1)
C(13)	26(1)	55(1)	35(1)	8(1)	-4(1)	2(1)
C(14)	29(1)	42(1)	58(1)	13(1)	-7(1)	2(1)
C(15)	34(1)	36(1)	58(1)	-8(1)	-3(1)	5(1)
C(16)	28(1)	45(1)	34(1)	-4(1)	0(1)	2(1)
C(17)	22(1)	20(1)	22(1)	0(1)	0(1)	-3(1)
C(18)	24(1)	29(1)	25(1)	-3(1)	0(1)	-3(1)
C(19)	35(1)	37(1)	31(1)	-10(1)	6(1)	0(1)
C(20)	50(1)	41(1)	24(1)	-9(1)	-1(1)	-4(1)
C(21)	40(1)	34(1)	28(1)	-1(1)	-11(1)	-3(1)
C(22)	28(1)	27(1)	26(1)	-1(1)	-5(1)	0(1)

Table 33 continued

	U11	U22	U33	U23	U13	U12
C(23)	20(1)	26(1)	22(1)	2(1)	-3(1)	1(1)
C(24)	25(1)	32(1)	31(1)	1(1)	-2(1)	-2(1)
C(25)	26(1)	42(1)	39(1)	10(1)	-2(1)	-9(1)
C(26)	21(1)	54(1)	34(1)	14(1)	5(1)	6(1)
C(27)	31(1)	42(1)	29(1)	5(1)	6(1)	12(1)
C(28)	27(1)	31(1)	28(1)	1(1)	1(1)	4(1)
C(29)	16(1)	24(1)	21(1)	0(1)	3(1)	-1(1)
C(30)	24(1)	24(1)	25(1)	-2(1)	-1(1)	1(1)
C(31)	30(1)	25(1)	30(1)	2(1)	1(1)	6(1)
C(32)	25(1)	38(1)	25(1)	6(1)	-3(1)	3(1)
C(33)	25(1)	35(1)	23(1)	0(1)	-2(1)	-7(1)
C(34)	24(1)	24(1)	22(1)	-1(1)	2(1)	-4(1)
C(35)	24(1)	22(1)	17(1)	-4(1)	1(1)	1(1)
C(36)	25(1)	25(1)	24(1)	-2(1)	3(1)	0(1)
C(37)	33(1)	31(1)	27(1)	-4(1)	7(1)	-7(1)
C(38)	53(1)	22(1)	26(1)	0(1)	8(1)	-5(1)
C(39)	46(1)	25(1)	27(1)	2(1)	-1(1)	8(1)
C(40)	29(1)	28(1)	25(1)	-1(1)	-2(1)	3(1)
C(41)	60(1)	39(1)	27(1)	-4(1)	5(1)	-6(1)

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